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ORIGINAL CONTRIBUTIONS

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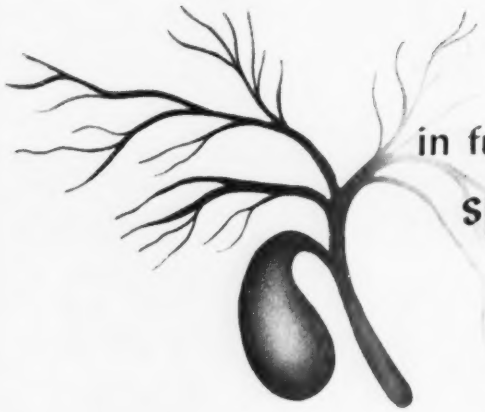

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1. Drabkin, D. L.: Metabolism of Hemin Chromoproteins, Physiol. Rev. *31*:345 (1951).
2. The Biosynthesis of Hemoglobin, Editorials, J.A.M.A. *150*:1223 (Nov. 22) 1952.

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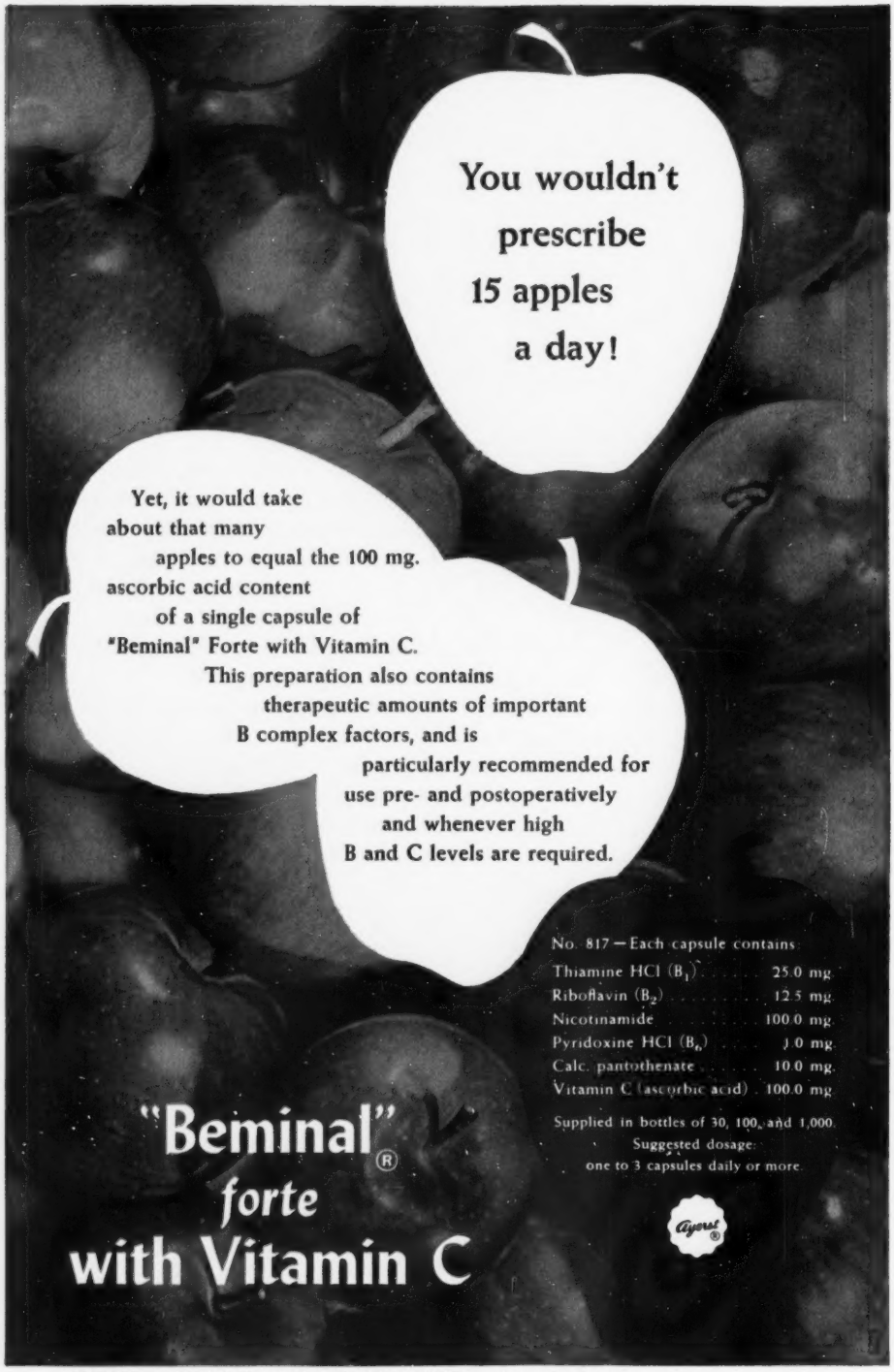

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1. Burnikel, R. H. & Sprecher, H. C.: Am. J. Dig. Dis. 19:191, 1952.
2. Marks, M. M.: Am. J. Dig. Dis. 18:219, 1951.
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4. Sweatman, C. A.: J. South Carolina M. A. 49:38, 1953.
5. Hamilton, H., in Trans. 5th Am. Cong. Obst. & Gyn., Mosby, 1952, p. 69.

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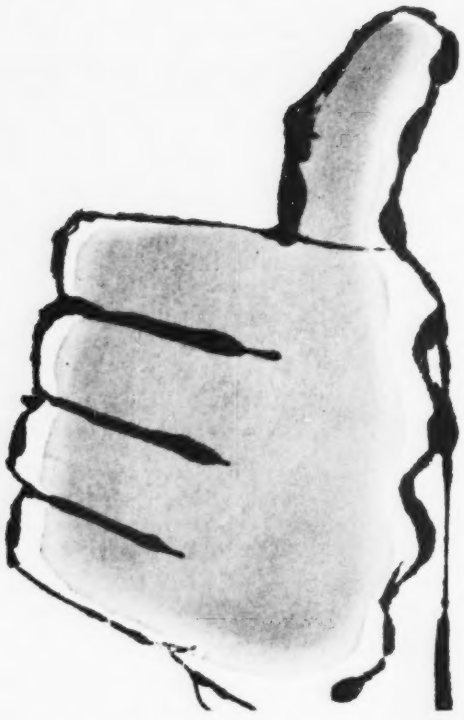

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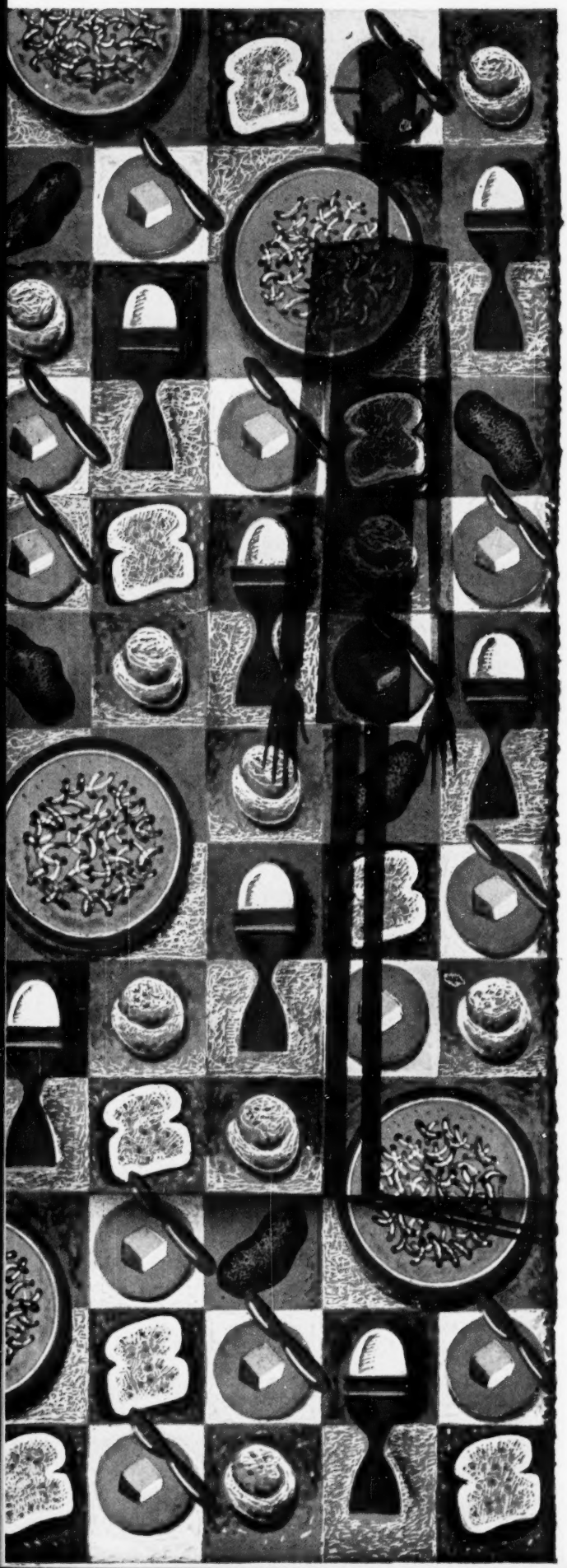

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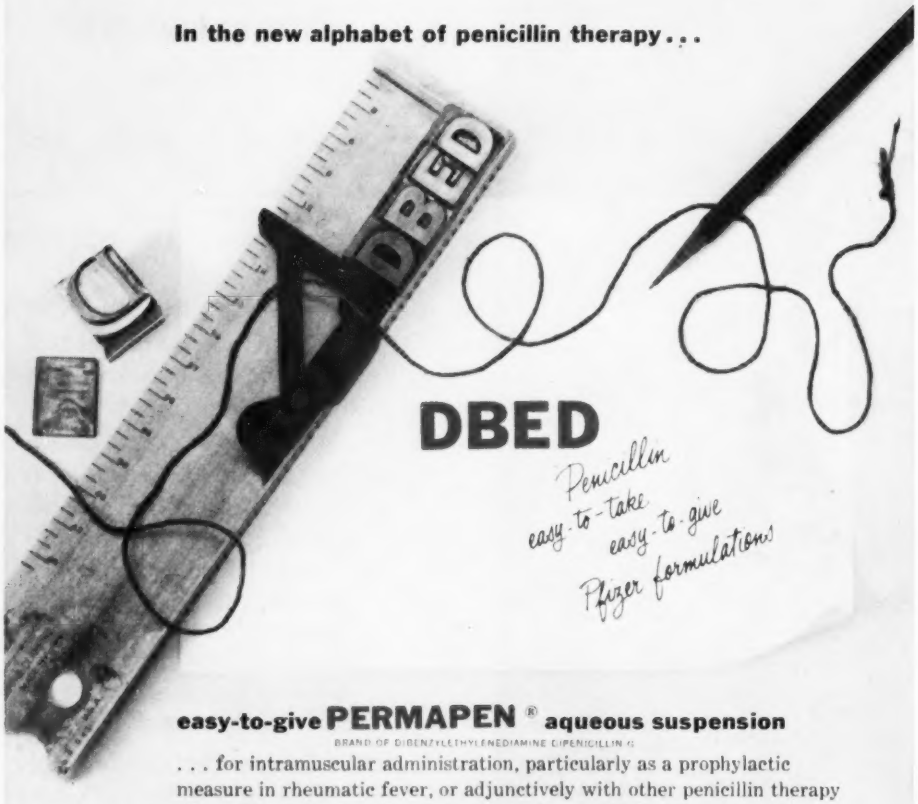

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PUBLIC HEALTH ASPECTS OF THE NEW INSECTICIDES

MORTON S. BISKIND, M.D. Westport, Connecticut

IN 1945, against the advice of investigators who had studied the pharmacology of the compound (70) and found it dangerous for all forms of life, DDT (chlorophenothane, dichlorodiphenyl-trichloroethane) was released in the United States and other countries for general use by the public as an insecticide. Contrary to popular opinion, DDT was not the first of the chlorinated cyclic hydrocarbons to be studied for its pesticidal properties, nor indeed is it the most potent compound of the group. In 1934, four years before DDT was introduced for this purpose in Switzerland, an American entomologist (17-19) reported on the insecticidal properties of the chlorinated naphthalenes, compounds shown shortly thereafter to be extremely toxic for man (53, 45).

Soon after the introduction of DDT for widespread use as a household, public health and agricultural insecticide, it became evident that virtually all forms of insects were propagating strains completely resistant to this compound. This led to a frantic search for more and more potent insecticides (which also turned out to be more and more toxic for animals and man). One after another new compounds were introduced, the total list being very long indeed. In addition to numerous variants of DDT itself, in widespread use appeared chlordane, toxaphene (chlorinated camphene), benzene hexachloride (hexachlorocyclohexane) and its gamma isomer, lindane (gammexane), heptachlor, and finally, going full circle, the incredibly deadly aldrin and dieldrin, both chlorinated naphthalenes (31, 33-37, 46, 52). In addition, the organic phosphorus compounds, closely related to the "nerve gases" of chemical warfare and lethal for man in minute doses, have also been widely used in agriculture—parathion, tetraethylpyrophosphate (T E P P), hexaethyltetraphosphate (HETP), malathion and others (22, 32).

In 1950, a year in which more than 200 million pounds of insecticides were used in agriculture alone in this country, investigators of the Federal Food and Drug Administration announced:

> "The finding of hepatic cell alteration at dietary levels as low as 5 p. p. m. of DDT, and the considerable storage of the chemical at levels that might well occur in some human diets, makes it extremely likely that the potential hazard of DDT has been underestimated." (68)

In 1951, the United States Public Health Service (49) pointed out:

> "DDT is a delayed-action poison. Due to the fact that it accumulates in the body tissues, especially in females, the repeated inhalation or ingestion of DDT constitutes a distinct health hazard. The deleterious effects are manifested principally in the liver, spleen, kidneys and spinal cord.
>
> "DDT is excreted in the milk of cows and of nursing mothers after exposure to DDT sprays and after consuming food contaminated with this poison. Children and infants especially are much more susceptible to poisoning than adults."

And the next year the U.S. Department of Agriculture (108) indicated that the chlorinated naphthalenes had been implicated as a cause of "X disease" (hyperkeratosis) in cattle, a usually fatal malady that has destroyed many thousands of animals in the United States in recent years (10,000 were reported from Texas alone in March 1953) (119). This represents not only a multimillion dollar loss to cattle-raisers but as will soon be evident, a serious hazard to the public that consumes meat, milk and animal fats. Just when chlorinated naphthalenes were first used in agriculture is not indicated in published reports (48), but it appears that they have been thus employed for some years and that they have been added to or have occurred as contaminants of other products used as insecticides. In addition they have been used for some time in lubricants (greases, cutting oils and crankcase oils)*—for what purpose is not made clear, and they have appeared in certain wood preservatives.

A number of remarkable features of the observations thus far reported on "X disease" deserve comment. The active agent has been found in wheat (59, 77, 87) (but the investigators say nothing about bread), and it is excreted in the milk. Calves fed on this milk develop the disease (nothing is said about babies** who drink such milk nor about those who eat the meat from these animals.) Cattle placed in a field in Indiana that had harbored others that previously had died of hyperkeratosis (1946 to 1949), developed the disease while cattle in an adjacent field were quite unaffected (114). All the investigators are extremely reticent about obvious and highly pertinent questions: Where did the wheat come from that contained the noxious agent? Was it sprayed or dusted in the field or exposed in storage to an insecticide, and if so, what? Were the cattle who originally developed hyperkeratosis on the farm in Indiana sprayed with insecticide, and if so, with what? Was the pasture likewise treated? The glaring omission of these data is not reassuring.

It is obvious from published material that the chlorinated naphthalenes are not the only chemical agents that can cause the disease. One such compound has tentatively been identified as trichlorobenzene (48). In view of the fact that in early studies on DDT in animals hyperkeratosis was observed (85), it seems very likely that this agent too is involved (9). And among the solvents used for DDT and related sub-

*The use of chlorinated naphthalenes in crankcase oils and other lubricants poses other public health problems: inhalation of these substances from motor exhaust on streets and highways and dermal absorption on the part of garage, service station and industrial workers.

**We have been accustomed for some time to a steadily declining infant mortality. But the over-all infant death rate increased in Metropolitan New York City in 1952 by 3 per cent. For economically less-favored groups the rise was 8 per cent. (Editorial: The City's Health in 1952, N.Y. Times, Jan. 14, 1953.)

stances are mixtures containing methylated naphthalenes. Since methyl groups may often be substituted for chlorine atoms in this variety of compounds, without loss of toxicity (16), these mixtures are at least suspect.

One insecticide solvent was indicated by W. C. Hueper (61) of the National Cancer Institute to have been found by other workers to be carcinogenic. One can only wonder why details of these findings have not been made available to the medical profession.

Since the last war there have been a number of curious changes in the incidence of certain ailments and the development of new syndromes never before observed. *A most significant feature of this situation is that both man and all his domestic animals have simultaneously been affected.*

In man, the incidence of poliomyelitis has risen sharply; there has been a striking increase in cardiovascular diseases, in cancer, in atypical pneumonias and especially interstitial pneumonitis in babies and children (58), in retrolental fibroplasia among premature infants, in conditions involving excessive fatigability and muscular weakness, in hepatitis and in obscure gastrointestinal and neuropsychiatric disorders often attributed to a new "virus" (or "virus X").

In animals, cattle have developed hyperkeratosis (or "X disease"), and the incidence of hoof and mouth disease has risen; hogs have vesicular exanthemata; sheep have "blue tongue," "scrapie" and "overeating disease;" chickens have Newcastle disease and other ailments; dogs have developed the so-called "hard pad" disease and the highly fatal "hepatitis X," and so on (43). With the obvious exception of hoof and mouth disease, not one of these conditions is mentioned in the comprehensive U. S. Department of Agriculture Handbook, "Keeping Livestock Healthy," published in 1942. This coincidence alone should have been sufficient to rouse a suspicion that something new that is common both to man and his domestic animals, has been operating in their environment during the period these changes have occurred. This new factor is not far to seek.

When in 1945 DDT was released for use by the general public in the United States and other countries, an impressive background of toxicologic investigations had already shown beyond doubt that this compound was dangerous for all animal life from insects to mammals. In rats, mice, rabbits, guinea pigs, cats, dogs, chicks, goats, sheep, cattle, horses and monkeys, DDT produces functional disturbances and degenerative changes in the skin, liver, gall bladder, lungs, kidney, spleen, thyroid, adrenals, ovaries, testicles, heart muscle, blood vessels, voluntary muscles, the brain and spinal cord and peripheral nerves, gastrointestinal tract and blood. The compound is equally dangerous to birds, fish, crustaceans, lizards, frogs, toads and snakes.***

Many of the beneficial predator insects like dragonflies, ladybugs and praying mantids may be even more susceptible to DDT than crop eating and other nuisance insects it is desired to kill. It was even known by 1945 that DDT is stored in the body fat of mammals and appears in the milk (106, 118). With this foreknowledge the series of catastrophic events that followed the most intensive campaign of mass poisoning in known human history, should not have surprised the experts. Yet, far from admitting a causal relationship so obvious that in any other field of biology it would be instantly accepted, virtually the entire apparatus of communication, lay and scientific alike, has been devoted to denying, concealing, suppressing, distorting and attempts to convert into its opposite, the overwhelming evidence. Libel, slander and economic boycott have not been overlooked in this campaign (21). —And a new principle of toxicology has, it seems, become firmly entrenched in the literature: no matter how lethal a poison may be for all other forms of animal life, if it doesn't kill human beings *instantly* it is safe. When nevertheless it unmistakably does kill a human, this was the victim's own fault—either he was "allergic" to it (the uncompensable sin!) or he didn't use it properly.

It is possible to consider in this article only a very small fraction of the total evidence as it has already filled many volumes and will undoubtedly fill many more.

It is not generally realized how vast are the quantities of the new poisons spread over the countryside in agriculture, used as sprays and aerosol fogs in mosquito control operations and applied in homes and gardens, in hospitals and other institutions, in food processing plants and retail establishments. In agriculture alone 232 million pounds were used in the United States in 1951 and 252 million pounds in 1952 (109); additional millions of pounds were of course used for the other applications. Herbicides of the chlorinated cyclic hydrocarbon group (e.g. 2, 4-D, 2, 4, 5-T) provide a further source of exposure. (In 1952, sale of pesticides in the United States amounted to 400 million dollars.)

Early in 1949, as a result of studies during the previous year, the author (9-11) published reports implicating DDT preparations in the syndrome widely attributed to a "virus - X" in man, in "X-disease" in cattle and in often fatal syndromes in dogs and cats. The relationship was promptly denied by government officials (12), who provided no evidence to contest the author's observations but relied solely on the prestige of government authority and sheer numbers of experts to bolster their position.

We had shown that exposure to DDT whether by inhalation, ingestion or absorption from the skin, leads to a bizarre syndrome which resembles other ailments in individual details but which had never been known to occur in its entirety prior to the introduction of the chlorinated cyclic hydrocarbon insecticides. This syndrome occurred repeatedly in hundreds of instances

***H. R. Mills (Death in the Florida Marshes, Audubon Magazine, Sept-Oct., 1952) has reported incredible devastation to wildlife in the sanctuary of the National Audubon Society in Tampa Bay, Florida, following aerial spraying with DDT for the control of mosquitoes. With each successive spraying the destruction of wildlife increased several-fold until the beaches were literally covered with dead fish and crabs. The concentration of DDT in the tissues of crabs analyzed after spraying in 1950 averaged 2.18 p. p. m. The next year after more sprayings the concentration of DDT in the crabs was 46 p. p. m. and the destruction of wildlife was proportionately faster and more extensive. Yet all this devastation was for naught, for, reports Mills, "None of the sprayings had any effect in mitigating the mosquito situation. Instead the mosquitoes increased until now they are more numerous than they were before the advent of DDT."

studied by the author following known exposure to DDT and related compounds and over and over again in the same patients, each time following known exposure. We have described the syndrome as follows (10-12):

The syndrome consists of a group of or all the following: Acute gastroenteritis occurs, with nausea, vomiting, abdominal pain, and diarrhea usually associated with extreme tenesmus. Coryza, cough and persistent sore throat are common, often followed by a persistent or recurrent feeling of constriction or a "lump" in the throat; occasionally the sensation of constriction extends substernally and to the back and may be associated with severe pain in either arm. In some cases the hyoid bone becomes acutely painful to pressure for a few days. Pain in the joints, generalized muscle weakness and exhausting fatigue are usual; the latter are often so severe in the acute stage as to be described by some patients as "paralysis." Sometimes the initial attack is ushered in by vertigo and syncope. Intractable headache and giddiness are not uncommon. Occasionally herpes zoster appears. Paresthesias of various kinds occur in most of the cases; areas of skin become exquisitely hypersensitive and after a few days this hyperesthesia disappears only to recur elsewhere, or irregular numbness, tingling sensations, pruritus or formication may occur. Erratic fibrillary twitching of voluntary muscles is common.

After subsidence of the acute attack, irregular spasm of smooth muscle throughout the gastrointestinal tract often persists for weeks or months, associated with increased fatigability, which only gradually regresses. Febrile reactions occur occasionally during the initial stages but are not the rule. Except for a tendency to anemia, and in some cases a relative lymphocytosis, no constant changes are observable in the blood. Many of the patients have an acute bout of apprehension associated with the foregoing symptom complex and rarely is this relieved by reassurance as to the absence of physical findings sufficient to account for the severity of the disturbance.

Most striking about the syndrome is the persistence of some of the symptoms, the tendency to repeated recurrence of others over a period of many months (some patients fail to show complete recovery even after a year) and the lack of detectable lesions sufficient to account for the severity of the subjective reaction.

By far the most disturbing of all the manifestations are the subjective reactions and the extreme muscular weakness. In the severe acute poisonings, patient after patient has used identical words, "I felt like I was going to die."

The sensation can perhaps best be described as one of unbearable emotional turbulence. There are at various times excitement, hyperirritability, anxiety, confusion, inability to concentrate, inattentiveness, forgetfulness and depression. Perhaps the one common phenomenon is extreme apprehensiveness. These episodes can easily be confused with anxiety attacks. The patients complain that they cannot keep their arms and legs still; they seem to "want to jump," and these phenomena may be accompanied by fine fibrillary twitchings. Disturbances of equilibrium may occur. Intractable headache and insomnia are frequent. Disturbances of the autonomic nervous system are likewise common: there may be attacks of tachycardia associated with dermal ischemia, sweating of the palms and a sense of impending syncope, followed by bradycardia, flushing of the skin, relaxation and cessation of palmar perspiration. (Whether or not disturbances of adrenal medullary function are associated with this phenomenon is a subject requiring further investigation.)

A characteristic of diagnostic importance, is the recurrence of the subjective reactions in "waves," as numerous patients have described it. Some have actually been able to clock the reaction with considerable precision from day to day. The reactions appear most likely to occur during periods of low blood sugar. Additionally, consumption of alcoholic beverages or acute emotional stress may provoke a severe exacerbation.

Often, patients with this disorder complain of a "hollow feeling" in the epigastrium which bears no constant chronologic relation to the ingestion of food, and in fact may occur immediately after a full meal. Attempts to eat further may provoke sharp repugnance for food and occasionally may lead to an attack of hiccups, or nausea. In other patients, actual overeating indistinguishable from the compulsive types seen in certain psychogenic disturbances may result.†

Hardly a single sensory nerve appears to be immune to involvement in this disorder: Paresthesias of every known variety, including disorders of vision, smell, taste, and hearing, may occur. Pain of varying intensity and duration may involve any area of the skin, may localize in a joint or even a tooth. Severe peripheral neuritis involving intense, protracted pain in one or more of the extremities is frequent. Pain in the inguinal region, usually bilateral, is also a frequent complaint; occasionally this may be referred to the genitalia. Virtually all these patients have striking diminution of vibratory sensation in the extremities. (This has repeatedly been observed in patients in whom readings had been taken on several occasions with the Collens vibrometer, prior to known exposure to DDT.) As already indicated, recurrent extreme fatigability is common. In acute exacerbations, mild clonic convulsions involving mainly the legs, have been observed. Several young children exposed to DDT developed a limp lasting from 2 or 3 days to a week or more.

Patients with this syndrome rarely show objective changes on physical examination sufficient to account for the severity of the subjective disorder and the actual amount of disability present. In addition to the change in vibratory sensation mentioned, enlargement and tenderness of the liver and palpable spasticity of the colon are the only findings which occur with any degree of constancy.

A characteristic history is that of a person (and in a number of cases, an entire family simultaneously involved) who, previously well and able to make a satisfactory emotional adjustment to his environment, suddenly is affected with the syndrome described and remains partially disabled for many months. In innumerable such cases it was possible to trace the onset of the illness to known exposure to DDT, usually from its use in the home.

Other investigators have also identified part or all of this syndrome with DDT poisoning. Wigglesworth (116), Case (28), Mobbs (82, 83), Pottenger and Krohn (91), Toomey (107), Arena (2), Stone and Gladstone (105), Knight (66, 67), Martin (80), Filkin (51), and numerous other observers have reported the occurrence of these cases following exposure to DDT and related pesticides. Pottenger and Krohn (91) have demonstrated the presence of DDT in the body fat of a large number of such patients, who showed in addition to the neuropsychiatric symptoms, hepatitis with low grade icterus and rise in blood cholesterol.

That this syndrome continues to be ascribed to a virus infection is indicated in a recent article by Dr. F. L. Mickle ("Connecticut Needs a New Virus Laboratory") (81):

> ". . . virus diseases which appear to be increasing are coming to the foreground. They are of much greater importance in the State than formerly. For instance, almost every person you meet on the street or in the homes of your friends speaks at one time or another of having had the 'virus that's going around' . . . these viruses cause distressing and incapacitating upper respiratory symptoms often accompanied by diarrhea and vomiting."††

†Note that, as already mentioned, there is now also an "overeating disease" of sheep.

††A factor that has led to considerable confusion in diagnosis is that DDT, for instance, produces mononuclear cell infiltration and splenic hyperplasia similar to that seen in genuine virus infections. This has been observed both in animals and in man.

Simultaneously with the occurrence of this disorder a number of related changes occurred in the incidence of known diseases. The most striking of these is poliomyelitis. In the United States the incidence of polio had been increasing prior to 1945 at a fairly constant rate, but its epidemiologic characteristics remained unchanged. Beginning in 1946 the *rate of increase more than doubled* (84). Since then remarkable changes in the character of the disease have been noted. Contrary to all past experience, the disease has remained epidemic year after year. It has largely lost its seasonal character, although still most prevalent in the Summer. More adults acquire the disorder than ever before. More cases of bulbar involvement are seen.

These changes have not been confined to the United States: For instance (54), "Until 1945, poliomyelitis was uncommon in Mexico. Since then, its incidence has been increasing; in 1950, nearly a thousand cases were observed in Mexico City . . . and the figures for the first half of 1951 seem to be higher."

In the Philippines and elsewhere in the Far East American troops, who used vast quantities of DDT as insecticides, had a high incidence of poliomyelitis, while it was extremely low in the surrounding native population (96).

In Israel (50), where the widespread use of DDT, especially in public health and agricultural applications, was delayed, "Prior to 1950 only one or two cases of poliomyelitis appeared monthly . . . During 1950, about sixteen hundred cases were listed, which is more than one case per thousand population. The epidemic was heralded by a rising number of isolated cases in the summer of 1950." It is recognized that a disturbed immunologic equilibrium as a result of mass immigration cannot explain this epidemic in Israel, any more than it can be a factor in Mexico or the United States. Curiously too in Israel (as in the case of the native populations in the Far East) the less technologically advanced Arabs have a much lower incidence of the disease.

McCormick (78), Scobey (100-101), and Goddard (57), in detailed studies, have all pointed out that factors other than infective agents are certainly involved in the etiology of polio, varying from nutritional defects to a variety of poisons which affect the nervous system.

Particularly relevant to recent aspects of this problem are neglected studies by Lillie and his collaborators (74, 75) of the National Institutes of Health, published in 1944 and 1947 respectively, which showed that DDT may produce degeneration of the anterior horn cells of the spinal cord in animals. These changes do not occur regularly in exposed animals any more than they do in human beings, but they do appear often enough to be significant. When the population is exposed to a chemical agent known to produce in animals lesions in the spinal cord resembling those in human polio, and thereafter the latter disease increases sharply in incidence and maintains its epidemic character year after year, is it unreasonable to suspect an etiologic relationship?

The mortality from cardiovascular diseases has also risen alarmingly since 1945. So serious is this problem that T. G. Klumpp (65) recently commented ". . . most businessmen . . . work with mental brakes set against their work and in mortal terror of a heart attack. They are afraid to live for fear of dying."

Among its numerous effects, DDT is a liver poison, an observation made by innumerable investigators. Associated with the induced hepatitis, there is hypercholesterolemia and hyperlipemia with an enhanced tendency to coronary atherosclerosis (13). Myocardial lesions have been reported in animals exposed to DDT as well as lesions of the blood vessels resembling periarteritis nodosa. In addition to changes in cellular enzyme systems leading to increased oxygen uptake (62, 93) similar to that produced by dinitrophenol, DDT also interferes with lactic acid metabolism and inhibits heart cytochrome oxidase (63). Finally, according to Lehman (71) of the Federal Food and Drug Administration,

> "DDT produces an excess excitability of the cardiac muscle so that any coincident sympathetic stimulation . . . can result in ventricular fibrillation."

In a recent publication purporting to disprove my contention that the insecticides are implicated in certain ailments, R. E. L. Fowler (55) of the U.S.P.H.S. Communicable Disease Center reported some statistics from the cotton belt of the Mississippi Delta, before and after the introduction of DDT. Mortality from "heart diseases" in this area rose from 141.3 before the use of DDT to 189.4 per 100,000 after its introduction (a rise of 34 percent!). But says Fowler, dismissing the subject, ". . . this was similar to the rise recorded for the state as a whole." Actually the figures he gives for the entire state are 170 per 100,000 before and 213.7 after DDT was used, an increase of 25.7 per cent! Surely this investigator could not have meant to imply that the population of Mississippi outside the Delta Area, was not significantly exposed to DDT. If the inhabitants of the Delta got an extra large dose, there is indeed an extra increase in cardiac mortality of 8.3 per cent to answer for it. The true difference is obviously even greater, for the comparison was not made between the Delta and the rest of the state but between the Delta and the whole state. (It is ironic that the statement by Klumpp already quoted appeared in the same issue of the same journal.)

With the known and secondary effects of DDT on the cardiovascular system, and the amazing increase in mortality from heart disease following widespread use of this agent, is it unreasonable to deduce an etiologic relationship?†††

†††W. J. McCormick in an excellent study (Clin. Med., 59:305, July, 1952) has recently implicated smoking of tobacco in the increasing incidence of coronary occlusion. Smoking has also been implicated in the rising incidence of cancer of the lung. Space does not permit an adequate discussion of the problem, but certain features of it appear to me to have been neglected. Despite the fact that prior to 1930 there were plenty of long-term intemperate smokers, cancer of the lung, for instance, was nevertheless a rare disease. Why was bronchiogenic carcinoma seen so rarely in chain smokers in the 1920's? Yet the evidence that smoking is today implicated in coronary thrombosis and in pulmonary cancer appears convincing. It is not generally realized that in growing tobacco, it is sprayed in the field with several of the DDT series of compounds, including the dangerous adrenal poison TDE (or "DDD"), chlordane, toxaphene and lindane and the

Fowler raises other issues but chooses not to discuss most of them—he gives no figures for the change in incidence of polio, nor in that of hepatitis. He does admit that absenteeism from school rose approximately 9 per cent during the period DDT was used, but he dismisses this as being possibly due to sociologic factors. He also indicates an increase in "communicable diseases" in the Delta area over that in the State as a whole but this he dismisses as being due to a racial difference (obviously this racial difference existed prior to the use of DDT).

The rise in the incidence of hepatitis in the general population since 1945 is also without parallel and involves all age groups, including young infants. Information as to total morbidity from this disorder is obviously unavailable but even a cursory survey of recent medical literature shows that hepatitis is now one of the major medical problems. Most of the reported cases are considered "infectious," although the virtual impossibility of diagnosing the "infectious" nature of a given case or of demonstrating the transmissibility of the disease must be obvious even to the casual observer, since human infectious hepatitis can be transmitted only to man. The most curious aspect of the rise in hepatitis is that simultaneously this has occurred for instance in cattle, in dogs and in other farm animals. In cattle "X-disease" (or hyperkeratosis) in which the chlorinated cyclic hydrocarbons are now etiologically implicated, involvement of the liver with a profound disturbance in vitamin A metabolism and storage is invariable. In dogs the highly fatal "infectious" hepatitis and hepatitis "X" have appeared.

It would be a most remarkable coincidence if several entirely different hepatic infective agents, each specific to a different animal species, arose simultaneously. Human infectious hepatitis is not transmissible to dogs or cattle or vice versa. How then account for this situation?

Without exception, every one of the chlorinated cyclic hydrocarbon insecticides is a liver poison. This is true of the entire series from the solvent monochlorobenzene and the mothicide paradichlorobenzene (4) to DDT and the chlorinated naphthalenes aldrin and dieldrin.† The chlorinated naphthalenes were shown to produce hepatitis (often with acute yellow atrophy) (45, 53) as long ago as 1936, and were responsible for much morbidity and many deaths among workers in industry (where they have been used in insulation for electric cable) long before these compounds were used in agriculture. Exposure to this whole group of compounds is now universal in the United States, and it appears that few persons escape storage of these toxic agents in the body fat.

The body fat has been termed a "biological magnifier" of DDT by investigators of the Federal Food and Drug Administration (68, 69). When amounts as low as 0.1 part per million dry weight (the average human diet contains very much more) are included in the diet, the body fat may reach concentrations up to 150 times as much. This has been confirmed by many workers on many species of animals. The significance and potential consequences of such storage in body fat have been reviewed in an excellent editorial in the Journal of the A.M.A., "Insecticide Storage in Adipose Tissue" (47). As pointed out in this editorial, body fat is not simply an inactive storage depot but is subject to continuous turnover and takes part in many metabolic processes. Further, "The influence of the stored insecticide may not be limited to adipose tissue. In fact, dichlorodiphenyltrichloroethane [DDT] is found in all other tissues in proportion to their fat content. Fats and lipids are constituents of cell membranes and are concerned with the phenomena of cell permeability and cell organization in every tissue of the body . . . Consequently storage of a toxicant in the fat of parenchymal cells is essentially storage in the cell itself, where such important enzymatic processes as oxidation, phosphorylation and cholesterol synthesis take place . . ."

What is the situation with regard to fat storage of insecticides in the human being? The difficulties involved in studying this problem are formidable. Quantitative chemical methods do not exist for all the com-

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organic phosphorus compounds as well. The residues of all these substances vaporize in the smoke.

Of course, still other factors may have operated even prior to the use of these compounds, such as changes in the composition of the tobacco plant from depletion of the soil, or use of certain fertilizers, or addition of certain substances in the final manufacturing process. Also, inhalation of other atmospheric contaminants which have increased in the last generation (e.g. lead, chlorinated naphthalenes and other products of combustion from motor exhaust), and the increased exposure to radiation (D. W. Moeller, et al.: Pub. Health Rep. 68:57, Jan., 1953) may well make the extra trauma of smoking the straw that breaks the camel's back. It is worth noting that *a sharp rise in the rate of increase in carcinoma of the lung occurred about 1947*, and this has persisted. It is interesting to compare charts showing the changes in the rates of increase of such diverse entities as poliomyelitis, retrolental fibroplasia, cardiovascular diseases and pulmonary carcinoma.

W. F. Enos et al. (J.A.M.A. 152:1090, July 18, 1953) have reported the startling observation that among 300 U. S. soldiers killed in action in Korea, average age approximately 22.1 years (range 18 to 48), 77.3 percent had "gross evidence of coronary arteriosclerosis" ranging "from 'fibrous' thickening to large atheromatous plaques causing complete occlusion of one or more of the major vessels." Last year Army Surgeon General Armstrong (J.A.M.A. 148: ad. p. 17, March 8, 1952) reported that among conditions of major concern to the service was acute hepatitis and that the incidence of neuropsychiatric disturbances was 54.1 per 1000 troops a year. Can these remarkable coincidences have anything to do with the fact that DDT and lindane are used in Korea intensively?

As for retrolental fibroplasia among premature infants, in New Jersey for instance, "... new cases of preschool blindness had been coming in at a rate of around 100 a year for the last three years; before that for two years the rate was less than fifty a year; and earlier, less than ten a year ... 75 per cent of the new cases were retrolental fibroplasia." (G. Meyer: Proc. Am. Assoc. of Workers for the Blind, reported in the N. Y. Times, July 15, 1953.) It is noteworthy that cataract was among the unfortunate consequences of the use of dinitrophenol as a thyroid substitute for weight reduction in the 1930's. Since, as already mentioned, DDT has been shown to produce an increase in oxygen uptake similar to dinitrophenol (93), and paradichlorobenzene has been reported also to produce cataract (4), is this phenomenon pure coincidence?

†Aldrin was recommended by the U. S. Department of Agriculture in 1953, for use on corn, wheat, oats, barley, rye, potatoes, peanuts, cotton, and on pastures. Dieldrin has likewise been recommended for corn, wheat, and other small grains, as well as for cotton and alfalfa. In the State of California dieldrin has been registered for use on alfalfa, apple, bean, cabbage, citrus fruit, corn, cotton, garlic, grape, melon, onion, peach, pear, and for treatment of wheat seed and outdoor use against house flies, mosquitoes, ants, chiggers, ticks and fleas.

pounds and the methods that are available, though accurate, are difficult, time consuming and laborious. Certain of the compounds are converted in the body to other substances before being stored. (Heptachlor, for instance, a constituent of chlordane which is also used separately, has been reported by F.D.A. investigators (40, 92) to be stored as heptachlor epoxide, *considerably more toxic* than the original heptachlor.) Obtaining sufficiently large fat specimens requires minor surgery, and only in lactating women can fat storage be estimated without surgery, since these compounds appear in the fat portion of the milk. In addition, numerous impediments of a nontechnical nature have been placed in the path of those who would pursue such studies on a sufficient scale. Nevertheless, the data that do exist, although limited thus far to studies on DDT, are the more alarming because they are derived from subjects in many widely separated parts of the country.

DDT has been demonstrated to occur in human body fat in all but a few of the cases examined (e.g., in sixty out of seventy-five in one series (69); in twenty-three out of twenty-five in another) (80) in concentrations from 0.1 to 34 p. p. m. (the highest result obtained—34 p. p. m.—came from an infant!). It has likewise been demonstrated in mother's milk (in seven out of seven cases in one series, in thirty out of thirty-two in another (11, 12, 69) in concentrations of from 0.01 to 116 p. p. m. In a study reported more recently from the U.S. Public Health Service (98), biopsy specimens were obtained from 113 volunteers from widely scattered sections of the United States. In 111 of these the range of DDT content was from 0 to 68 p. p. m., with an average concentration of 6.41 p. p. m. (The significance of this figure may perhaps be appreciated by the fact that as little as 3 p. p. m. has been found to inhibit heart cytochrome oxidase.) Two DDT handlers had 91 and 291 p. p. m. respectively! Even after prolonged rest from their occupations (in the first case, two years) the DDT levels in the fat were still 30 and 240 p. p. m., illustrating the tenacity with which this material is stored. A further study by workers at the United States Public Health Service (88) showed, in eight specimens of human fat, from 1.9 to 14 p. p. m. DDT and from 1.7 to 44.7 p. p. m. of a compound tentatively identified as DDE (an ethylene derivative of DDT). These investigators point out:

> "Presumably the DDT occurring in the fat of individuals of the general population arises mainly through contamination of a number of common foodstuffs. It is not known whether the DDE evidently present is also a contaminant as a result of partial degradation of the DDT residues on plant products prior to ingestion, or whether degradation occurs during digestion or after deposition in the fat."

This study has unfortunately been used as propaganda for the alleged safety of DDT on the assumption that it shows that DDT is detoxified in the body, hence is virtually harmless (104). The observations, already cited, that the related compound heptachlor is converted in the body to a *more* toxic substance points up the inadvisability of drawing such far-reaching conclusions from inadequate data. Quantitative studies on the occurrence in human body fat of other insecticides to which there is universal dietary and environmental exposure, such as technical benzene hexachloride and its individual isomers, toxaphene, methoxychlor, chlordane, heptachlor, aldrin and dieldrin are as yet not available, although qualitative evidence of human storage of benzene hexachloride has been obtained and evidence of fat storage of the other compounds is available from animal investigations.#

Contamination of foodstuffs (e.g., 3, 5, 6-8, 24-27, 31, 38, 42, 64, 79, 95, 103, 110, 117) provides probably the main source of the chlorinated hydrocarbons found in human body fat, although this is by no means the only source. These compounds are used as sprays, aerosols and fogs in inhabited areas in such manner that the finely dispersed particles are readily absorbable through the lungs and through the skin, they are vaporized by means of heating devices in homes, restaurants, food stores and other buildings; they are incorporated into paints, wallpaper and floor wax; they are used to mothproof virtually every variety of textile, including many that no moth larva could eat; they are sprayed and painted on every conceivable surface in homes and institutions. As the Canadian Department of National Health and Welfare (29) has pointed out, "Dangerous residues of these compounds may persist on treated surfaces for very long periods." Obviously, once used, finely dispersed vapors and dusts of so stable a character readily become resuspended in air, can be inhaled directly over long periods and can contaminate foods and food utensils. Contact with treated surfaces can lead to significant absorption through the skin. The amounts required to produce severe acute reactions in human beings are often extremely small. In one case investigated by the author, the syndrome described in detail earlier in this article was produced by the ingestion of only four micrograms of DDT in food.

Unfortunately, today contamination of food is virtually universal. Even if the farmer does not use the new insecticides (and few do not), it is a rare food that escapes contact with insecticides in storage, shipment, processing plants, warehouses and stores.

Dendy (44), for instance, bought milk and meat on the open market in Texas, from July through December. Every specimen of these staples was found to contain DDT, from less than 0.5 p. p. m. to 13.8 p. p. m. in milk and from 3.1 p. p. m. in lean meat to 68.5 p. p. m. in fat meat. Corn and sunflowers were sprayed in the field with DDT, toxaphene, chlordane, BHC, methoxychlor, or aldrin using less than standard agricultural practice. In every case the insecticide penetrated to the interior of the kernels or seeds and was present in concentrations of from 4 to 7.4 p. p. m.

Numerous other studies both on market samples of foods bought at retail, and on specimens obtained by duplicating standard agricultural practice, show that

#It has been claimed that certain compounds, like methoxychlor (an analog of DDT containing methoxy groups in place of two chlorine atoms), are less toxic and less likely to be stored in body fat than DDT. But if the liver is first damaged by another toxic agent, methoxychlor produces symptoms similar to those of DDT and stores in the body fat from 10 to 100 times as much as in control animals. (Laug, E. P., and Kunze, F. M.: Fed. Proc., 10:318, March, 1951.) (Cf. also, Haag, H. B., et al.: Arch. int. de Pharmacodyn. et de Therap., 83:491, Sept., 1950.)

it is a rare food that escapes contamination with amounts often greatly in excess of that known to produce liver damage in animals.

It has been claimed that without the use of newer insecticides, there would not be enough food to go around and that even though these substances are toxic, their use involves a "calculated risk." But as a number of agricultural and public health workers have now recognized, even disregarding toxic effects on the human population, the use of the newer insecticides is not only not helpful, but in the long run actually detrimental, both for the growth of crops and the prevention of disease carried by insect vectors. Everywhere that DDT has been used for any length of time, strains of insects, both those that attack crops, as well as flies, mosquitoes and lice, have become resistant not only to DDT but to related compounds as well. This has been shown to be caused by the long persistence of the toxicity of these compounds. The phenomenon never occurred so long as only short-acting insecticides like pyrethrum and rotenone were employed (30).

A. D. Pickett (89, 90) in Nova Scotia, and Paul DeBach (41), in California have both pointed out that the use of preparations like DDT in orchards, for instance, by creating insecticide resistance and by destroying natural predators of the noxious insects, *actually perpetuates the emergency* for which these compounds were used in the first place.

As many workers have now shown, by maintaining proper fertility of the soil, it is possible without the use of insecticides to raise crops showing little or no damage from insects (1, 20, 115). It must be remembered that agriculture flourished for thousands of years without the use of insecticides and that even today the average yields per acre for many crops grown without these chemicals in other countries greatly exceed the average yields in the United States.

Owing to the insoluble problems created by insecticide resistance in public health applications, A. D. Hess (60) of the U.S. Public Health Service Communicable Disease Center, has advocated a return to biologic methods and the older technics of sanitation for the control of insect vectors. The futility of the chemical approach to the insect problem is perhaps no better illustrated than by the fact that after seven or eight years of the most intensive imaginable poison campaign, virtually the entire "bread basket" area of the United States was blanketed in 1953 with army worms, that destroyed vast areas of food crops, over many states. It was admitted by the U.S. Department of Agriculture that further chemical attack on these insects was fruitless, although this same Department then released the extremely toxic dieldrin for use against them! (112).

The extremely stable nature of the DDT group of insecticides poses another problem. In amounts normally used for growing of crops, severe poisoning of the soil (39, 76, 99, 102, 111, 113) has persisted for the entire duration of reported observations (seven years) and as no means are available to destroy these compounds, millions of acres of farmland may ultimately have to be withdrawn from cultivation, since these substances not only inhibit the growth of many plants but may be absorbed into the food portions in dangerous concentrations.

Two widespread practices deserve special comment; the use of chlordane in homes (73), institutions and food establishments (94) and the similar use of electric vaporizers for DDT or lindane (the gamma isomer of benzene hexachloride) or a mixture of the two.

Chlordane is probably the most commonly used for roach control in buildings of all the available insecticides. It is routinely used even in hospitals. Chlordane, a technical mixture with a musty odor, consisting mainly of chlorinated indanes (heptachlor, already mentioned, is one of the constituents), is an extremely dangerous nerve and liver poison. Although very persistent when applied, it is nevertheless slowly volatilized. Frings and O'Tousa (56) report in studies on animals:

> "The first system affected is the nervous system, and nervous symptoms predominate in acute toxicity. In chronic intoxication, however, the liver seems to be most affected . . . Because of the widespread use of chlordane in structural pest control, the rather striking toxicity of the vapor is significant . . ."

Lehman (72) recently reported experience with chlordane at the Federal Food and Drug Administration:

> "In my opinion, chlordane is one of the most toxic of insecticides we have to deal with . . . it penetrates the skin very readily. Therefore, anyone handling it could be poisoned. Or if it is used as a household spray, the potential hazard of living in these houses is quite great because of the ability of chlordane to penetrate the skin and because of the volatility of the insecticide and the possibility of poisoning by inhalation. More to the point is that it is very toxic to the liver and kidneys . . . I would put chlordane four to five times more poisonous than DDT . . . I would hesitate to eat food that had any chlordane on it whatsoever . . . It is our opinion that chlordane has no place in the food industry where even the remotest opportunity for contamination exists.** We feel that its use as a household spray*** or in floor waxes is out of place . . . we have not been able to maintain pigeons in a small room that was treated with chlordane, even after a thorough scrubbing with strong alkali and subsequent airing for several weeks."

Exposure to chlordane leads to rapid, high and tenacious storage in body fat. Heptachlor, one of its components, as already mentioned, is converted in the body to a more toxic substance, heptachlor epoxide, and stored as such.

The use of chlordane against termites in the foundation of a house, in a case brought to my attention, re-

**As an example of the use of these materials in the food industry, Holmes and Salathe (Proc. Am. Chem. Soc. 115th meeting, 1949, p. 18A) state: "Experience has shown within the baking industry that DDT and chlordane can be applied safely in 5 & 2 per cent solutions respectively . . . the application must be so general that there are few if any areas that insects might travel over, which have not been treated." (!)

***In 1952 a popular journal of immense circulation advised its readers to apply chlordane to floors, baseboards, sinks, under refrigerators and other appliances, to mattresses, wallpaper, rugs, clothes closets and clothing.

sulted in such a high vapor concentration that the house remained thereafter uninhabitable to the owner. All efforts to remove the offending agent failed.

In a hospital in which technical chlordane is applied routinely in the kitchen and food storeroom and less regularly elsewhere in the institution, for roach control, an epidemic of hepatitis has persisted among the resident nursing staff for three years. This disorder was considered "infectious,"** yet despite adequate epidemiologic precautions the cases continue to appear. The chlordane is still in use.

During the past two years or so an incredible profusion of devices for vaporizing insecticides in room air have appeared on the market. These vary from thermostatically controlled heating devices, to special electric light bulbs with a compartment for inserting a pellet or crystals of DDT or lindane, to metallic gadgets and even impregnated adhesive tape for application to ordinary light bulbs. The hazards of these devices have been pointed out repeatedly, yet newspapers and magazines promote them to the public as if they were the safest of all the new miracles. A newspaper of international repute even carried an article in which it was pointed out, referring to such a device, ". . . it is easy in using it to increase the rate of vaporization to the point where it is hazardous to humans . . . the experts advise that products containing lindane be used with the utmost precaution. One goes so far as to say that: 'Although they're advertised as safe, they are really not'." Yet the same issue and succeeding Sunday issues carried numerous advertisements for them.

To quote the A. M. A. Council on Pharmacy and Chemistry (35),

> ". . . it is not reasonable to expect that human beings can avoid injury if they are exposed . . . year after year to a toxic agent in atmospheric concentrations that kill insects in a few hours . . . the resultant injury may be cumulative or delayed, or simulate a chronic disease of other origin, thereby making identification and statistical comparison difficult or impossible."

It was found that, in an eight hour period an average person might inhale from 1.3 to 13 mg. of DDT or from 0.9 to 2 mg. of lindane, as ordinarily vaporized from one of these devices. In addition, the vaporized material ultimately recrystallizes on walls, ceilings, furniture, clothing, on food utensils and food.

The California State Board of Health (23) passed a resolution last year,

> ". . . that electrical vaporizers dispensing lindane or other chlorinated hydrocarbons be not used in closed spaces where people sleep, work or where unpackaged*** food is exposed, and that extreme caution be exercised in the indoor dispersion of such chemicals by any means . . ."

The Federal Interdepartmental Committee on Pest Control has also advised that insecticide vaporizers not be used for insect control in living quarters.

TREATMENT

Treatment of poisoning with the chlorinated cyclic hydrocarbons of the DDT group requires *both* elimination of further exposure from environment and food, and treatment of the associated nutritional defect which accompanies the hepatitis. Sprayed clothing, textiles and bedding must be cleaned with lipoid solvents, the particles of DDT must be removed from the room dust in places that have been treated with DDT aerosol, preferably by lacquering, painting or waxing (with wax that is insecticide-free, of course!) all affected surfaces. Wall paper impregnated with DDT has caused severe symptoms in a number of cases investigated. Persons sensitive to DDT and related compounds must avoid as much as possible visiting places known to have been treated with these agents. Foods or portions of foods in which DDT and the like are now known to occur must be avoided. This entails avoidance of butterfat in all its forms, careful peeling of all fruits and vegetables and avoidance of those that cannot be peeled, substitution of fish and seafood and skim milk products as much as possible for the usual sources of protein, and the *medicinal grade* of peanut oil (which we have found to be free of the DDT group of compounds) for the usual sources of fat.

Repeatedly, I have had patients who lost weight continuously to the extent of 20 or 30 pounds on a full diet containing large amounts of beef and butterfat, who promptly regained all or most of their weight on a diet lower in calories but restricted as indicated. Unless further exposure to the newer insecticides is avoided as stringently as possible, both from direct contact or inhalation and from food, no remedies I have tried give any except slight symptomatic relief. (Pentobarbital in small—30 mg.—doses often temporarily relieves the symptoms related to the nervous system.)

As Pottenger and Krohn, and we have found, administration of intensive, complete and persistent nutritional therapy is essential in these cases to repair the liver damage. A source of the available water-soluble and lipo-soluble vitamins, suitable oral liver products and linotropic factors, together with a high protein diet, are all necessary to adequate tissue repair. The requisites for this type of therapy have been discussed in detail elsewhere (15).

**Aside from the question of the nature of "viruses," which is too intricate to consider here (cf. reference 78 and 101, for instance), it should be pointed out that not only may a toxic agent which damages a particular organ simulate infectious disease, but the damaged organ is more susceptible to transmissible agents, if exposure occurs.

***It is unfortunate that the California Board did not also include *packaged* food. The U. S. Department of Agriculture has reported the following experience: "An unexpected finding was the contamination of raisins stored for one month in boxes treated with DDT on the outside only, which indicated that DDT could be spread by volatilizing. This idea was substantiated by analyzing grain samples that had been in storage three to four months in elevators that had been treated with DDT when empty." (A procedure incidentally which the Department of Agriculture still recommends!) (Toxicity of Insecticides, Fungicides and Herbicides, p. 45.) A similar experience was reported from Britain. When wheat flour, soya flour, ground nuts or coca beans were stored for from four to thirteen months in sacks treated with 1 per cent or 5 per cent DDT (the amounts found necessary to prevent insect penetration) all these products absorbed DDT in concentrations of from 5 to 645 p. p. m. (G.V.B. Herford: J. Roy. San. Inst., 70:666-673, Nov., 1950.)

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GRADUATED CLINICAL PRE-DETECTION OF DIGESTIVE TUMORS. INITIAL RESULTS OF THE FIRST SYSTEMATIC DETECTION CENTER.

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IT HAS BY now become commonplace to stress the frequency of digestive cancers and the importance of their early diagnosis: we shall not therefore deal here with the remarkable progress which has been made up to the present time in the social organization of the fight against cancer, whether as a result of fitting out centers for study and treatment or the intensification of anti-cancer propaganda or the creation of insurance funds against cancer designed to ease the financial burden of long and costly treatments. In addition to this first problem, there exists another one which has to overcome special difficulties: *the systematic detection of cancer in social communities.*

In the case of digestive tumors, in which those of the stomach preponderate, systematic detection in communities may be said to have been made possible since the time R. A. Gutmann, followed by his pupils, arrived at the only practical solution for the early diagnosis of gastric cancer by describing the radiological aspects suggestive of its onset, the radioclinical method and the therapeutic test. Only then was there a hint of what the solution to the second problem might be. The terrible latency of digestive tumors, which is the main cause of their late discovery, is well known: however, cancers which are absolutely latent are far less numerous than cancers with attenuated symptoms. The great expense which systematic radiological examinations would involve makes it impossible to organize detection for all the healthy members of a community; but it would be possible to urge patients suffering from minor symptoms to visit the Center at an early stage of the evolution of their illness. We give this method the name of *clinical predetection in several stages.*

M. Parturier-Albot has in our opinion the merit of having made the first assay of this kind based on the principle of graduated clinical predetection of digestive tumors: in 1937 he organized, within the framework of the Federated Friendly Societies of the Seine, a systematic detection service for gastric tumors in only those chronic dyspeptics whose complaint was obviously not benign; the results obtained in 1938, 1939 and during the first four months of 1940 (interrupted at this period by the war) were reported in 1941 by M. Parturier-Albot (32).

Here we shall deal with the social aspect of various attempts at methodical organization for the detection of digestive tumors in the community, and we shall compare the results of the different methods employed with those which we have obtained in France.

PRINCIPLES OF SYSTEMATIC DETECTION

Any organization for systematic detection rests on one fundamental principle which may be interpreted differently according to the tendencies of the organizers and the nature of the complaint they wish to detect.

In digestive tumors, and especially in cancer of the stomach, the dilemma is the same and some tests have involved all members of a community whilst others have only involved individuals selected from their group by pre-detection: but the criterion for selection varies according to the method.

1st. Mass radiological examinations.

It comes of course to the mind to carry out systematic radioscopic or radiographic examinations of whole sections of the population particularly susceptible to gastric cancer, that is of people over 40 years old. This method, valid for tuberculosis, does not work in the case of cancer (Kirklin & Hobson). Thus after the first attempt of M. Parturier-Albot, already mentioned but of which many American authors appear ignorant, there have been in America many attempts to overcome this difficulty but with less satisfactory results. F. Roach, R. Sloan, R. M. Morgan (Baltimore) place high hopes in the fluorographic methods. However, the worst criticism one can level at all these methods of systematic radiography of subjects not preselected is that the proportion of cancers detected is infinitely small, as G. Albot, M. Parturier-Albot and G. Gordet (1) proved in 1943.

Their results have been confirmed by contemporary

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and later tests. The rate of detection is 3 per 1,000 for Collins, Govers & Dorn (1941) and also for Kirklin & Hobson (1948). It is only 3 per 2,400 for Saint-John, Swenson & Harvey (1948) who discovered 2 cancers and 1 gastric lymphocarcinoma. The rate is nil for Dailey & Miller (1945) in spite of an examination of 500 subjects. Roach, Sloan, Morgan (1949) were more satisfied since they detected one cancer per 700 men and per 1,200 women examined: in all, for 10,000 subjects of both sexes seen during one year, they found 12 cancers, or 1.2 per 1,000.

2nd. Various methods of selecting patients for pre-detection.

A. Radioscopic pre-detection.

It was proposed to examine radioscopically a series of patients and only retain for radiographical pictures those whose radioscopy appeared suspicious. This struck us as being a very bad method. We have known for a long time that incipient gastric cancers are "infra-radioscopic": by examining radiographically only patients whose stomach was suspected after radioscopy, there is a risk, or rather a certainty, that all incipient cancers will be overlooked.

B. Biological pre-detection.

It was proposed in order to overcome the difficulty presented by radiological examinations which are so long, minute and costly, to carry them out only where indicated after a study of the gastric fluid or where anemia is confirmed.

By the *cytological study of the gastric fluid* according to Papanicolaou's method, Cooper, later Fremont, Smith, Graham & Meigs (1948, Vincent Memorial Laboratory) tried to discover who should undergo radiological examination. However, the difficulty of anatomo-pathological diagnosis by means of isolated cells should be stressed and despite the importance of this method, it can in no way serve as a systematic *detection* method for communities for at the present time it is too fallible and too costly.

The same applies to the systematic study of *gastric* hypochlorhydria. According to Comfort & Kelsex (1934), it is possible, to a certain extent, to predict which patients are likely to develop gastric cancer later. One ought therefore to view hypochlorhydric and anachlorhydric patients with suspicion in regard to gastric cancer and in their cases carry out regularly systematic radiographic examinations. It seems to us however that such a practice would exclude from the detection of cancers those who have still a normal secretion, and they are numerous. Furthermore, it is not clear how to practice repeated examinations of gastric chemistry on such a large scale and make them acceptable to subjects apparently in good health.

Of the stages leading up to cancer, certain *anemic conditions* have been stressed (in particular anemia due to atrophic gastritis). In fact, however interesting this may be, this idea is open to discussion. Rigler & Kaplan (1948) admit that cancer occurs 20 times more frequently in those suffering from anemia than in the rest of the population. (They find 8% cancer out of 211 cases of anemia). State, Varco & Wangensteen find no cases of cancer in 79 anemic patients in 1947: but in 1949, examining 92 cases of anemia they discovered 3 cancers. But Chevallier (1950) shows that it is impossible to assert that anemia follows, accompanies or precedes gastric cancer.

As for *systematic gastroscopy*, it is not clear how it can be made acceptable on a large scale. Gastroscopy, even in the hands of the most competent, also has its shortcomings especially when the cancer is in its incipient stages.

3rd. Clinical pre-detection in several stages.

In the present state of affairs the pre-detection of cancer of the stomach can only be clinical.

It is by always considering it as a possibility when faced with apparently the most ordinary symptoms that the doctor will successfully prevent an incipient cancer eluding him; equal responsibility for failure to recognize the early stages is shared by the patient who shows no sign of alarm and by the careless doctor. One cannot therefore wait until the patient becomes alarmed and seeks a consultation. *An examination for detection must be instigated when the slightest disorders occur.*

Systematic radiography of all dyspeptics who "might have a cancer" represents a superior system of pre-detection to those we have just mentioned; but this method is still too costly and its yield too slight. It is necessary for this systematic radiological examination to be preceded by a second selection carried out among dyspeptic patients in order to eliminate all those who have a clearly defined affection which is not maligant: only *those patients who have aroused suspicions or those whose affection is not clearly defined* will be sent on to the detection center: this *second stage* of clinical pre-detection calls for the introduction of a first group of doctors. The tumor detection center, with its team of specialists grouped around one or several experts, constitutes the *third stage* in which detection proper takes place. One of the original features of our method of detection lies in the fact that we have endeavored to make use of *all the budding organization of social medicine* and to interest in our detection campaign doctors in control of social insurance, factory doctors and doctors in medical centers undertaking systematic examinations. The initial results of this method were reported in 1941 by M. Parturier-Albot. From the 5th of January 1944 to the 1st of January 1946, our detection center for digestive tumors functioned at the Federation of Friendly Societies of the Seine and the results of this second attempt, published in November 1944 detected unrecognized cancer at the rate of 1 per 33 patients examined. From January 1st, 1946 the same center has been functioning on the premises of the Local Social Security Office of the Paris region.

RECRUITMENT FOR THE CENTER

Our patients come from medical examination consultations, from doctors in charge of panel patients, from factory doctors and also from city doctors.

When the diagnosis has once been established the "panel doctor" and the treating doctor each receive a detailed account of their patient's case with diagnostic conclusions and eventually, treatment suggestions.

Much more so than the general practitioner, the

TABLE I—GASTRIC CANCERS

Stage	No.	Name	Age	Duration	Dominant disorders Nature	Localization	Development
	1	Raf. . . . Léon	54	2 yrs. 6 mths. 6 mths.	Regurgitation Cramp, vomiting, diarrhea, emaciation Therapeutic test — no more disorders	Prepyloric lesser curvature	Gastrectomy 26.6.48 —keeping well
I	2	Mat. . . . André	32	5 yrs. 2 yrs.	Late appearance of epigastric heaviness Emaciation	Horizontal lesser curvature	Gastrectomy 17.11.51 —keeping well
	3	Pell. . . . Roger	38	2 yrs. 3 wks.	Burning sensation, diarrhea Sharp daily attacks of burning sensation	Greater curvature	Gastrectomy July 1947 —keeping well
II	4	Bail. . . . Pierre	43	10 yrs.	Heaviness, emaciation, asthenia	Prepyloric lesser curvature	Gastrectomy 14.12.50 —keeping well
	5	Belti. . . . Achille	54	2 yrs.	Ulcer syndrome	Angle of lesser curvature	Gastrectomy 3.7.48 —keeping well
	6	Mer. . . . Joseph	62	8 yrs. 9.9 mths.	Burning sensation, intermittent heaviness Daily attacks of pain, anorexia, asthenia	Prepyloric lesser curvature (transformed ulcer)	Gastrectomy 16.9.48 —keeping well
III	7	Bill. . . . Berthe	52	6 mths.	Cramp, diarrhea, distention, flatulence, emaciation	Prepyloric lesser curvature	Gastrectomy 10.10.48 —keeping well
	8	Hoeb. . . . Georges	51	4 yrs.	Pain in sharp attacks, constipation, anorexia, emaciation	Prepyloric lesser curvature (clear from 1st year)	Gastrectomy 14.5.49 —keeping well
	9	Pri. . . . T.	41	1 yr.	Anemia, asthenia, emaciation	Horizontal lesser curvature	Gastrectomy 15.12.52
	10	Ther. . . . Jules	79	years 1 yr.	Ulcer syndrome Daily cramps	Antrum	Not operated on
	11	Soir. . . . Jean	61	2 mths.	Epigastric discomfort, diarrhea, emaciation	Greater curvature	Gastrectomy 27.12.47 — died
	12	Talb. . . . Louis	63	years 9.9 mths.	Diarrhea and constipation Vomiting, emaciation	Antrum	Gastroenterostomy — died
	13	Amoud. . . . Léon	65	years 6 mths.	Epigastric heaviness Post-prandial pains	Upper stomach	Gastrectomy 22.3.50 — died
	14	Lamar. . . . Charles	67	1 yr. 9 mths.	Heaviness Dysphagia	Lesser curvature affecting pylorus & esophagus	Inoperable
IV	15	Gies. . . . Louis	37	4 yrs. 9.9 mths.	Ulcer syndrome Continual pains and tumor	Antrum	Operation refused
	16	Charp. . . . Louis	70	1 yr.	Vomiting, diarrhea, asthenia	Horizontal stomach	Inoperable
	17	Lur. . . . Henri	62	6 yrs. 6 mths.	Burning sensation, emaciation Vomiting	Antrum (Lacuna & niche)	Operation refused
	18	Vib. . . . Marie	74	2 yrs.	Burning sensation, regurgitation	Angle (virole)	Inoperable
	19	Tup . . . Henri	75	years 2 mths.	Heaviness Delayed pains, burning sensation, vomiting	Angle (virole)	Inoperable
	20	Call. . . . Gustave	58	2½ yrs.	Burning sensation	Vertical & horizontal lesser curvature	Inoperable (Parkinson)
	21	Baud. . . . Robert	53	1 yr.	Heaviness	Angle of lesser curvature	Operation refused
	22	Bloch	83	years 6 mths.	Heaviness Diarrhea, anemia	Horizontal stomach	Inoperable
	23	Fra. . . . Odette	34	3 yrs.	Delayed pains	Horizontal lesser curvature	Gastrectomy 15.12.52

panel doctor is an important cog in the wheel of our organization. Actually, in virtue of his post he assesses the medical card of the insured person. It is possible for him to draw attention to the disparity existing between an illusory medical treatment and the serious condition of the patient, and up to him to suspect underlying organic lesions which in the absence of radiographies or on account of "poor radiographies" would have eluded a town doctor.

It happens then in a great number of cases that the patients whom we are called upon to assess are *patients already selected by medical teams who have eliminated those who are quite clearly not suffering from cancer.*

This clinical pre-detection method has been perfected since the appearance of the *medical examination service,* which institutes district medical examinations (if desired by those summoned to attend). Here it is a case of real preventive medicine. At the end of a first exploratory examination, a card is made out in duplicate (one copy for the examinee which is if necessary passed on to a competent specialist). The gastroenterological specialists of the medical examination service have the task of judging, from a single series of radiographies, whether the cases are of a functional or organic nature, whether it is a sure case of ulcer or of a probable lesion: they eliminate immediately lesions which are clearly benign or clearly malignant and send the "suspected" patients to our Tumor Detection Center.

One group alone escapes this clinical pre-detection, those alarmed by "anti-cancer propaganda." It is well known that posters, pamphlets are sent to factories in big industrial centers and to local authorities, that talks are organized on the radio. Anti-cancer propaganda as a method of detection remains mediocre and unprofitable as patients all believe that they are not concerned. Those alarmed by the "propaganda" are often those with a phobia, sometimes people touched by the fact that a near relative has had cancer, and the proportion of cancers detected in these cases is infinitely small. However we did once detect a cancer in the case of one of these patients where despite the extremely poor clinical symptoms, just for good form we asked for pictures of the stomach.

Our system then leads to the concentration of numerous examinations on a single patient under suspicion instead of dispersing diagnostic effort over a great number of patients chosen at random. The suspected patient becomes the focal point of many radiological examinations, if required. The clinical method of R. A. Gutmann may then be put into practice however many radiological examinations are considered necessary.

It will be observed that this system concentrates all the attention on early diagnosis of cancer of the stomach. It is nevertheless true that at the same time we endeavor to detect other digestive cancers. We ask our associates to suspect cancer of the esophagus and of the cardia when faced with slight dysphagic disorders. We ask them to send us systematically all the patients showing signs of intestinal disorders, hemorrhage, small lesions in the ano-rectal region suggestive of cancer of the colon or of the rectum.

ORGANIZATION OF THE CENTER

At present the center comprizes two consultations whose function is strictly identical. The head of the consulting service has at his disposal an assistant chosen from experienced gastroenterologists.

It is important to note that these examinations for detection are performed in a manner very different from that of the usual consultation in gastroenterology. The assistant takes down observations on patients, examines them and decides what radiographies to take; it falls to him therefore in practice to play the modest role of a medical student or of a dresser; but it should however be made clear that, for very many patients, this interrogation and this examination will be the only ones and will not be taken up again by the head of the consulting service: that is why it is necessary for the assistant, although his part seems so modest, to be a doctor very well versed in gastroenterology and in the systematic detection of cancer. In the same way, the radiological examinations which, from a pecuniary point of view cannot be repeated, must be carried out by a radiologist or by a gastroenterologist with a sound knowledge of the methods and habits of the consulting service.

With few exceptions, the specialist judges from the

TABLE II. CANCERS OF THE RECTUM

Group	No.	Name		Age	Development
A	1	Rob. . .	M	64	Electrocoagulation 1950. Cured for 2½ years
B					
C	2	Bon. . .	F	59	Babcock 13.8.1952—keeping well.
	3	Chen. . .	M	58	Amputation Oct. 1950—no news.
D	4	Bap. . .	M	45	Resection 8.9.1947—no news
	5	Gal. . .	F	55	Resection 25.1.1951. Died end of 1951.
	6	Fer. . .	M	63	Refused operation—died.
	7	Muz. . .	F	64	Refused operation—died 1 year later.
	8	Char. . .	F	63	Amputation 14.10.1950—died March 1952.
	9	Sam. . .	M	71	Resection 19.10.1949. Relapse Feb. 1950—died
	10	Lebl. . .	M	77	Refused operation—died 1 month later.
	11	Lem. . .	M	53	Resection 18.4.1950—died same evening.
	12	Sai. . .	M	45	Amputation Nov. 1949—keeping well.
	13	Pro. . .	M	50	Refused operation—died 1 year later.
	14	Ta. . .	M	61	Amputation April 1946—died within the month
	15	Mer. . .	M	73	Amputation 16.10.1951—died on the 18th day.
	16	Bel. . .	M	71	Counter irritant 5.3.1951—died 21.9.1951.
	17	Ces. . .	F	42	Refused operation 1949; oper. Dec. 1951—died
	18	Ma. . .	F	60	Operation deferred (phlebitis)

case sheet, from reading the questionnaire and a typed copy of the clinical examination by his assistant and from scrutiny of the radiographies which have been performed. He can then in the majority of cases eliminate immediately benign lesions (ulcers, gastritis, etc. . .) and also lesions which are clearly malignant (extensive cancerous lesions). It is only in special circumstances and in difficult cases that he asks to see the patients and questions them himself. Quite often, when faced with suspected lesions whose nature it is however impossible to determine as yet, he puts off until a later date a new radiological examination (1 month or 2 according to the case) and asks the doctor treating the case to assist him in carrying out a "therapeutic test."

This method of working is very special and involves a possible risk of mistakes which we will not attempt to hide: also the interrogation and the radiographies must be carried out with the greatest care by trained specialists who are used to working with an expert. But on the other hand, this method has the advantage of being rapid, relatively economical and efficient. Now experience has shown us that, provided there is team work, with assistants of whom the head of the service is absolutely sure, mistakes occur no more frequently than in the practice of ordinary gastroenterology in hospitals.

Statistical Results

Our statistics for the years 1946-1947-1948-1949-1950-1951-1952 are the following:

Out of 2,819 patients seen for the first time, 20 patients must be subtracted—whose cancer had been diagnosed by the doctor treating them or by the consulting doctor of the Local Social Security Service and who had come to the detection center exclusively for advice on treatment or for confirmation of the diagnosis.

Out of 2,799 patients remaining, the center detected 57 with cancers:

— 23 cancers of the stomach: 15 were operated on; 8 were inoperable or refused the operation.
— 23 cancers of the rectum, of the anus and of the sigmoid and cecum.
— 9 cancers of the esophagus and of the cardia.
— 1 cancer of the liver.
— 1 cancer of the pancreas.

Despite the modest appearance of the figures, the detection involved is considerable: it is the most valid of the methods which have appeared up to now in the way of social detection of tumors of the digestive system. The fact is directly connected with the method of detection which far from being systematic is graduated. If we bear in mind the proportion of cancers detected, we see that it is 20.3 per 1,000 and that, to state it simply, one unrecognized cancer has been detected for every 50 patients examined.

Although the numbers used for these calculations are too small to have an absolute statistical value, they seem to us to be worth recording. They are lower than those in our first statistics drawn up from January 1st 1944 to November 15th 1944 as published in 1944: in this first trial period 138 patients suffering from digestive disorders were examined and 4 gastric cancers detected, one of which was very small: this would give a proportion of 28 detections per 1,000 and of 1 case of cancer for each 34 patients examined. This is an insufficient number of patients on which to base this first statistic and we consider the present figures as nearer to the truth.

Our figures then are superior to those given by the American authors mentioned above and this at less cost.

General Information

1. Gastric cancers.

Our cancers of the stomach can be grouped (cp. Table 1) according to the nomenclature proposed by R. A. GUTMANN & G. ALBOT in:

Stage 1.—Epithelioma of the mucous membrane: 3 cases.

	Name	*Age*	*Duration of disorders*
1.	RAF. . .Léon	54	2 years
2.	MAT. . .André	32	5 years
3.	PELL. . .Roger	38	several years
	Stage 2. Epithelioma in initial stages: 1 case.		
4.	BOUL. . .Pierre	43	10 years
	Stage 3. Cancers only slightly evolved: 5 cases.		
5.	BELTRAM. . .	54	2 years
6.	MER. . .Joseph	62	8 years
7.	BILL. . .Berthe	52	6 months
8.	HOEB. . .Georges	51	4 years
9.	PRL. . .T. . . .	41	1 year
	Stage 4. Large cancers: 14 cases.		
10.	THER. . .	79	several years
11.	JOIR. . .	61	2 months
12.	TALB. . .Louis	63	several years
13.	AMOUD. . .Léon	65	4 years
14.	LAMA. . .Charles	67	1 year
15.	GIES. . . .	37	6 years
16.	CHARPENT. . .	70	several years
17.	LUR. . .	62	1 year
18.	VIB. . .Marie	74	2 years
19.	TUPIN. . .	75	several years
20.	CALL. . .Gustave	58	2½ years
21.	BAUD. . .Robert	53	1 year
22.	BLA. . .	83	several years
23.	FRA. . .Odette	34	3 years

The majority of the patients sent to us were subjects who had been *sufferers for a number of years.* Suspicion was borne in upon a controlling doctor for example of the contrast between the different medical treatments followed and the absence of results, or between the very nature of the functional disorders and the absence of radiological examination.

Never did we observe in a patient all the usual symptoms of gastric cancer, but rather a single symptom put us on the track.

Anorexia (cases 6 and 8) and asthenia (case 1) rarely appeared. Emaciation can be a very early symptom (case 1) but it is more often so in cases already well advanced (cases 7,8,11,12,13 and 22).

We must stress the frequency with which a gastric cancer is revealed beneath deceptive manifestations of intestinal symptoms. Certainly, R. A. Gutmann has stressed for a long time the intestinal forms of gastric cancer, but their frequency seemed remarkable

to us. Diarrhea was a dominant symptom in cases 4, 7, 8, 11, 12, 14 and 22, that is in 7 cases out of 23; whilst constipation seemed rarer (1 case only, no. 8). Often intestinal disorders take on the appearance of ordinary farinaceous dyspepsia with its distended abdomen and flatulence: these cases, despite the apparent banality of the symptoms, when associated with some slight epigastric pains should be considered as suspicious and a systematic series of gastro-duodenal exposures as well as the colic transit should be asked for.

As for ordinary pseudo-ulcerous dyspepsia, we have not found it particularly frequent: it only existed in 4 cases out of 23 (cases 5, 8, 10 and 13): it is interesting to note that contrary to a recently expressed opinion, cases no. 1, 2, and 3, the ones diagnosed the earliest (cancers of the mucous membrane) have never given pseudo-ulcerous symptomatology. Anemia revealed it in 2 cases (case 9 and 22).

All our cases (except cases 7 and 11) underwent a long evolution before being detected; they ought to have been detected sooner (except for the first 9), but without our aid they would have been discovered even later. Cases 7 and 11 are exceptions: case 7 was quickly detected after 6 months of painful development (the patient was operated on and was still alive 4 years later). Case 11 seems to have been latent for a long time and would have evolved considerably in 2 months.

2. Cancers of the esophagus.

The problem of cancer of the esophagus presents itself in a different way of course: it should be considered when faced with any dysphagia, even apparently spasmodic. Our efforts in this direction have been disappointing up to now since all our cases, with one exception, have ended in death, either because the patient was inoperable or because of a relapse after the operation. We have not counted among our triumphs of detection a patient suffering from gastric ulcer in the process of healing, whom we diagnosed as having an incipient cancer at the mouth of the cardia: after operation it was shown that it was only a matter of a polyadenoma not yet transformed!

3. Cancer of the rectum.

We do not intend to expatiate on the systematic detection of cancer of the rectum which seems to us both possible and rewarding but which is at present still dangerously neglected.

We tried to send for a systematic *rectoscopic examination* all patients suffering from ano-rectal disorders of a banal appearance: hemorrhoids, fistulas, fissures, anal pruritus, diarrhea. Out of 2,834 patients examined and used for general statistical purposes, 1,329 belong to this very special group. In these 1,329 patients we detected 18 cancers of the rectum, that is 13.5 per 1,000.

We will class them according to the nomenclature recommended in 1951 by M. Parturier-Albot (33) and which has the advantage of taking into account the therapeutic possibilities in each variety, A, B, C, D, (cp. Table II).

Group A (incipient cancer of small dimensions, apparently mucous, superficial, movable and supple): 1 case.

Group B (slightly vegetating cancer resting on a supple, scarcely indurated base): 0 cases.

Group C (a more infiltrated cancer resting on a cardboard like base): 2 cases.

Group D (large infiltrating cancers, adhesive, circular or ulcerated cancers): 15 cases.

Of 18 patients between the ages of 42 and 85, 12 were operated on; 4 were under 60 and 8 over 60; 5 refused the operation.

All 4 patients under 60 operated on died within a lapse of time ranging from 1 day to 1 year later. Of 8 patients over 60, 6 died. The patients who refused the operation died within a lapse of time ranging from 6 to 18 months.

In short, the operatory mortality rate seems enormous. The reason must be sought in the fact that out of 18 unrecognized cancers, 15 were voluminous cancers of the type D, adhesive and circular, having passed beyond the metastatic stage, lymphatic and therefore all doomed to fatal issue. Of the others 3 were small cancers, 2 of which healed surgically and 1 incipient cancer of the type A easily cured by very widespread electro-coagulation.

It is therefore striking that so many patients should be followed up and treated without being examined by rectal touch or by rectoscopy in the false security of an erroneous diagnosis of hemorrhoids. It must then be repeated to satiety that only *systematic rectoscopy* of all patients showing even slight ano-rectal symptoms enables cancer of the rectum to be detected. Even a slight loss of blood, a recent constipation, a temporary diarrhea, a recent attack of flatulence, a slight discharge, a simple pruritus should indicate the need for an endoscopic examination. When diarrhea and repeated loss of blood become regular, when tenesmus occurs it is already too late and the infiltrating tumor has a good chance of attacking the lymphatic system: even if the general condition is apparently good, the part already has a fair chance of being lost however skilful the surgeon may be. Finally, just as cancer of the stomach can have an atypical symptomatology and be revealed by deceptive and intestinal symptoms, so cancer of the rectum sometimes takes on the appearance of symptoms of the transverse or ascending colons, or even epigastric pains, vomiting and nausea, sometimes even a gall-bladder symptomatology—and *this notion still remains unknown.* It is in this way that one of our cancers of the rectum was accidently detected during the medical examination of a patient with symptoms of the upper right quadrant.

Before we detected them, 17 cases out of 18 had a long and unrecognized evolution and ought to have been recognized a long time before.

CONCLUSION

Judging from several years experience, there would seem to be not only a theoretical but also a practical possibility of organizing the systematic detection of tumors of the digestive system in communities. This organization can be sufficiently economical and obtain sufficiently important results on condition that it has the help of "graduated clinical pre-detection."

The pre-detection consists of examining by radiology and by complicated and costly examinations only patients who have first been selected. Selection, by radioscopy, by tubing, by diagnosis of anemia, does not

seem practical to us. On the other hand, graduated clinical pre-detection has henceforward proved its worth. It consists of having the patients selected by successive medical teams. The first stage involves isolating healthy individuals from those with dyspeptic, ano-rectal or even slight intestinal disorders. The second stage consists of eliminating from this first group all patients who are clearly suffering from a non-cancerous complaint and of sending to the detection center only those whose symptoms suggest cancer or those whose complaint cannot be classed definitely as benign.

It is possible to forecast an eventual intermediate stage designed to eliminate from these patients clear cases of tumor in order to keep for the detection center only those whose diagnosis is delicate. This supplementary stage may be found in the gastroenterological section of the "Systematic Medical Examinations."

In any event, it is around a concentrated group of patients that the technical and financial effort of the detection center should gravitate. Under these conditions, the proportion of cancers detected in relation to the number of patients examined becomes much larger than with other methods, reaching 20.3 per 1,000 instead of 1 to 3 per 1,000; that is 1 cancer detected for every 50 patients examined.

All this organization is simple if one is ready to take advantage of the whole machinery of social medicine (control of social insurance benefits, factory medicine, medical examination). It should of course be open to practitioners and our confident collaboration with them increases from year to year.

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GASTROJEJUNOSTOMY (A new approach to an old operative procedure)

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Part I

THE OPERATION from the beginning has had many changes in the method of performance. Professor Billroth's assistant, Anton Wolfler (1), in his Vienna Clinic in 1881, performed it successfully.

In America, the first recorded operation of gastroenterostomy was performed in Cincinnati, Ohio. The record of this case was found in the magazine called "The Polyclinic," Vol. VI, No. 8, Philadelphia, February, 1889, entitled:

"Gastro-enterostomy
a clinical lecture by
Joseph Ransohoff, M. D., F.R.C.S. Eng.,
Professor of Anatomy, Medical College of Ohio,
and Surgeon
to the Cincinnati and Good Samaritan Hospital."

The patient had a cancer of the stomach and vomited continuously, resulting in a loss of weight. On December 31, 1889, Professor Joseph Ransohoff operated on the patient. It was decided to perform a gastroenterostomy. Decalcified bone plates were used for coaptation. Only four sutures were inserted, yet coaptation was very accurate. The operation lasted only 35 minutes instead of 1½ to 2 hours required by the old method. The mortality of this operation was 50%. More exact details of the operation were not given.

Many articles since this have been written about results and techniques of the operation. The men who made the greatest contribution to procedures and operative techniques were Von Haeber, the Mayos, and Lord Moynihan of London, England. Today the technique described by Lord Moynihan in his volumes on abdominal surgery is the one most generally used in this country.

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In performing the operation, as described by Lord Moynihan, it was found that these patients many times vomited and had rather marked intolerance for fluids and food. For many days decompressant methods had to be used to avoid distention of the stomach. It was felt that there must be an anatomical and physiological explanation for this result.

An intense study was made of the anatomy of the stomach correlating the motility and physiology. At this time, by pure coincidence, a patient was being gastroscoped and the gastroenterostomy opening was visualized. This, one is very rarely able to do. It was

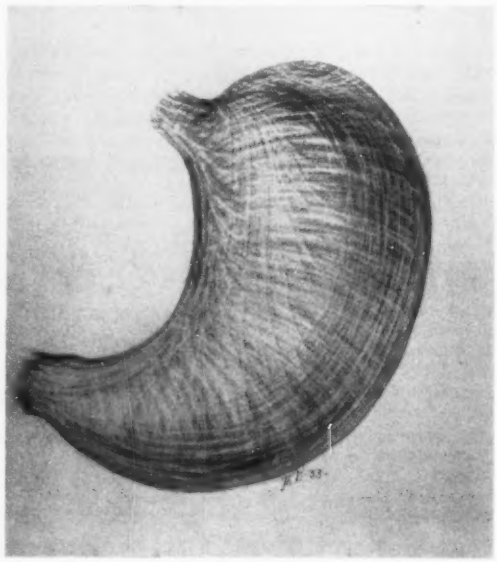

Fig. 1.

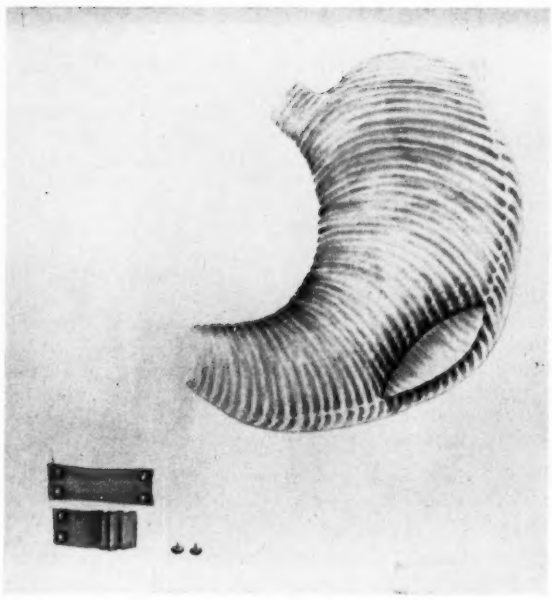

Fig. 2.

seen that the gastroenterostomy opened very slightly when the peristaltic wave went over it. This suggested that, to function properly, the emptying through the gastroenterostomy depended upon the increased intraluminal gastric pressure. This, we felt, was the real reason why the gastroenterostomy opening many times did not function early following operation. Not until the degenerative process of the cut muscles occurred at a later time, was it possible for it to function. With the above evidence we felt that gastroenterostomy operation should be changed to hasten this proper function.

The normal anatomy of the stomach must now be studied to better understand the anatomical-physiological basis that makes the operation successful.

The normal stomach has the following distribution of its musculature in three layers. This is a description given by Cunningham Manual of Practical Anatomy, ninth Edition, Vol. 2, Page 301.

"The muscular coat is arranged in three layers of non-striped muscle and in that respect differs from other parts of alimentary tube, which have only two—an outer longitudinal and an inner circular. Stomach has an outer, a middle, and an inner.

"*Outer layer* is composed of longitudinal fibers which are continuous with the longitudinal fibers of the oesophagus and the duodenum. They are best marked along the curvatures, while along the middle of each surface, the layer is absent or exceedingly thin. At the pylorus some of the deeper fibers bend inward into the substance of the sphincter, and probably serve to open the pyloric orifice when food is sent through it.

"The *middle layer* is a complete layer of circular fibers. They are continuous with the circular fibers of the oesophagus. In the pyloric canal, a thickening of the middle layer begins and gradually increases until the pylorus is reached, where it is accentuated to form the sphincter, and then abruptly diminishes—the outer fibers only being continuous with much thinner circular layer of the duodenum.

"The *inside layer* is incomplete and is made of oblique bundles of fibers that hang in inverted loops from the right part of the fundus. The lateral bundles fan out towards the greater curvature as they descend; the medial bundles descend along the lesser curvature forming two fairly definite muscular ridges on the anterior and posterior walls. These ridges lie in the folds

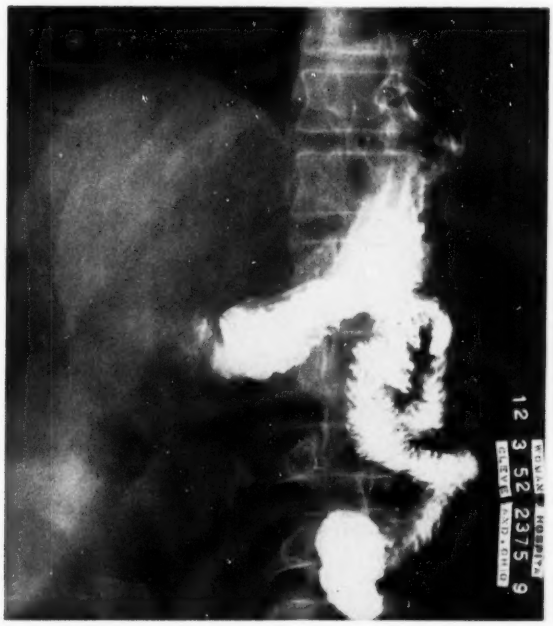

Fig. 3.

Fig. 4.

Fig. 5

of mucous membrane that run along the lesser curvature, and when they contract they bring the edges of these folds together, correcting the groove between them into a canal." (Fig. I.)

Analyzing this anatomical evidence the placing of a cut on the posterior wall, in fact parallel with circular fibers, would not open when a peristaltic wave would move down the stomach.

Professor Todd, Professor of Anatomy of Western Reserve, years ago, stated that the lesser curvature was relatively the fixed portion of the stomach. The lesser curvature is also the magen-strasse or pathway of the stomach. It is possible for a person with a full stomach to drink water, which by-passes the food, going directly through to the duodenum.

Now let's change the gastroenterostomy opening to the greater curvature. It may be placed close to the pylorus or higher towards the cardiac end. What happens to the peristaltic wave as it passes over the stomach? The different layers are using the lesser curvature as a semi-fixed point. The stomach contracts like a ring towards the pylorus. Cut crosswise the oblique fibers and the circular fibers which are the strongest and thickest fibers of the stomach now separate the longitudinal fibers. What changes occur in its motility? The stomach contracts normally until it comes to where the greater curvature was cut for two or more inches. The circular fibers being the strongest muscle of the three layers and cut crosswise, they will retract when a peristaltic wave passes over and in this manner open the gastroenterostomy stoma widely. (Fig. II.) This is confirmed in the x-ray, which is directly opposite to what happens in the usually performed gastroenterostomy operation. (Fig. III.)

Technical Method of Performing This Modified Gastrojejunostomy. A new approach to an old operative procedure.

The stomach has been decompressed by Levine suction at least eight hours before surgery.

The usual right rectus, midline, or left rectus incision is used. The abdomen is explored and correct indication found for performing a gastrojejunostomy.

In the most dependent part of the stomach the gastrocolic omentum is removed from the stomach by multiple clamping, cutting, and ligating the blood vessels. In this way one enters the greater omentum bursa. At least three to four inches should be mobilized. (Fig. IV.) The transverse colon is raised and in an avascular place in the mesocolon a point is selected to the right or left of the middle colic artery. An incision is made through which the greater curvature of the stomach previously mobilized from the gastrocolic omentum is brought. (Fig. V.) Usually we do not use clamps to perform this operation. The operative area is packed off with sterile tapes.

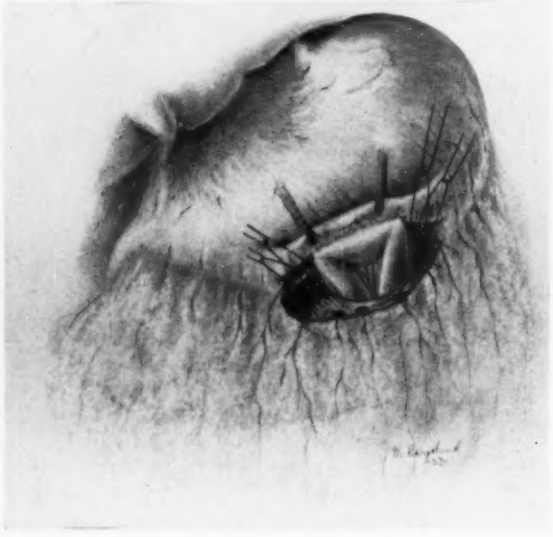

Fig. 6.

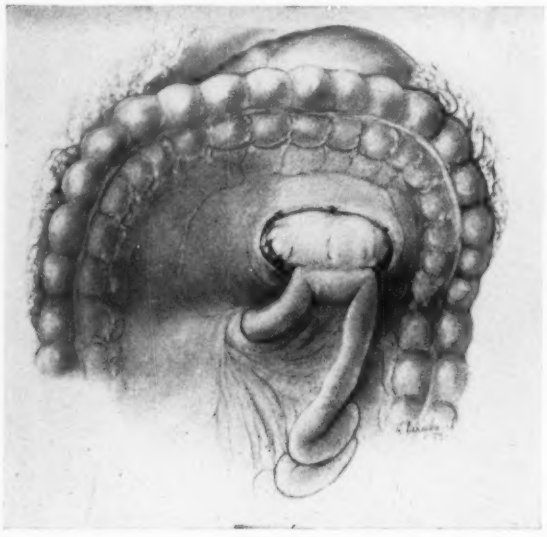

Fig. 7.

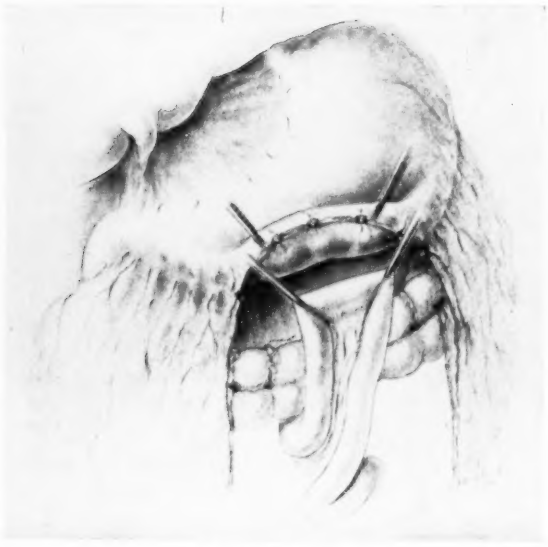

Fig. 8.

Using a short loop of the jejunum the right side of the greater curvature is attached by interrupted sutures to the afferent proximal loop of the jejunum and the left side of the greater curvature to the efferent distal part. (Fig. VI.) Then the serosa is attached by interrupted silk sutures. The sutures are started slightly posterior to the middle of the antimesenteric border of the jejunum. Then a sharp knife cuts the serosa of the jejunum down to musoca the determined length. Then the stomach serosa down to the mucosa is cut and these cut edges are sewed together as is usually done by interrupted #00 silk. All bleeders are tied by #00 plain catgut.

The following procedure to open the mucosa is used either with knife or scissors or cautery, cutting on a Kocher dissector. The fluid in the stomach is aspirated.

Fig. 9.

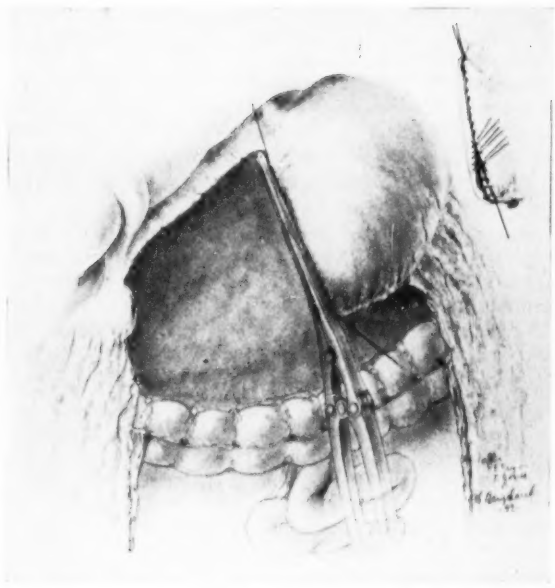

Fig. 10.

The mucosal layer is brought together using #00 chronic catgut on an atraumatic needle. The left side is started by going within, out, and tying around the previously held long silk suture. Then the mucosa is united by a locking stitch, continuous, until the mucosa is brought together. Then very fine close interrupted silk #00 is used making a tight anastomosis. Then the mesocolon slit is attached around the anastomosis as is usually done in a gastroenterostomy. The opening in the gastrocolic omentum is closed above with a few sutures to prevent any possible hernia. (Fig. VII.) The abdomen is closed without drainage in the usual manner in layers by chronic catgut sutures, silk or cotton, as desired by the operator.

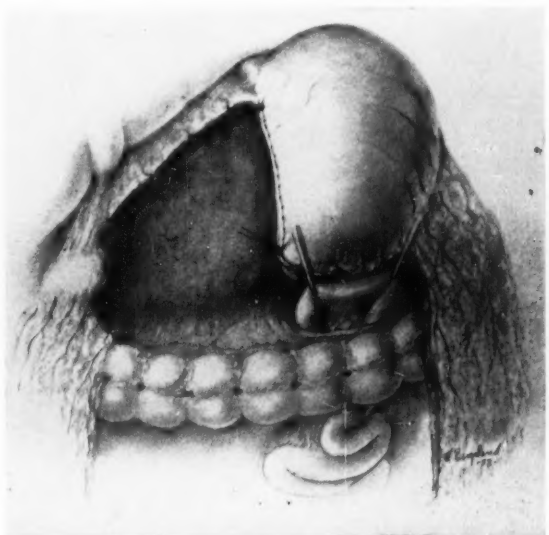

Fig. 11.

The preceding operative technique shows the method of retrocolic gastrojejunostomy. Figs. VIII. and IX. show the anticolic method of performing the same operation. The area of the omentum on the greater curvature, the amount of omentum and gastrocolic omentum removed is just large enough to permit the anastomosis. Any area which might permit hernia to take place into the greater omental sac is closed by silk sutures.

Postoperative care of the patient is no problem at all. The same day of the operation water in small amounts is taken hourly; the next day milk and water, half and half; and the following day cereals. No Levine tube is needed and the patients very rarely even vomit and very rapidly are on a full diet. This is in contrast to the older method of Levine suction and restricted diet for days and even a week.

The following series of cases performed by this method and results will be reviewed in table form.

Indication	*Diagnosis*	*Results*	*Mortality*
Obstruction	Cancer of Stomach, 16 cases	Symptomatic relief	None
Obstruction	Ulcer of Duodenum, 4 cases	Symptomatic relief	None

Discussion of Results: This modification of an old operative procedure based on anatomical structure, and physiological basis, improves the results materially if the strict indications for gastrojejunostomy are followed.

Part II.

SUBTOTAL GASTRECTOMY

(A new approach to the operation by the use of a simplified technique)

A surgeon interested in gastric surgery will often first perform a gastrojejunostomy. After this technique has been mastered, the next step is a subtotal gastrectomy for cancer. One of the standard procedures such as Billroth I or II type of gastric resection, or the two Polya types, is usually followed. Other modifications may be used. The surgeon finds that the technique must be exacting in the different phases of the operation for, unless completely mastered, the operation carries a high mortality. Even if the techniques are mastered some are still difficult to perform and time-consuming. We have performed many types of gastric resections meticulously but have followed the Finsterer-Hofmeister technique most often. Professor Finsterer was my professor and taught me many techniques used in gastric surgery.

We felt that if the operative time could be shortened easily it would be a real advance in gastric surgery.

Following the work in Part I on Gastrojejunostomy we felt that the same principles should be applied to gastric surgery, making it an easy and safe procedure.

Technique used in performing the new type of subtotal gastrectomy.

The mobilization of the gastrocolic omentum and lesser curvature omentum does not differ from the usual technique. After the duodenum is mobilized for an inch and a quarter to an inch and a half, the duodenum is clamped about ¾ inch beyond the pylorus by two Penner crushing duodenal clamps or Ochsner clamps. A cautery is used to sever the duodenum. Following this there is a difference in the closure technique. Starting below the lesser curvature, under the crushing clamp, a chromic #00 catgut on an atraumatic needle is sutured through and through and tied in the beginning. When the greater curvature has been reached the clamp is removed. Using this same suture the greater curvature is purse-stringed and inverted by a smooth forceps. The same suture is continued over and over, inverting the middle part of the duodenum until the lesser curvature is reached. It is then purse-stringed and inverted, thus closing the duodenum. The duodenum end is inverted again by lateral interrupted silk sutures giving a 3-layer closure. The gastrocolic

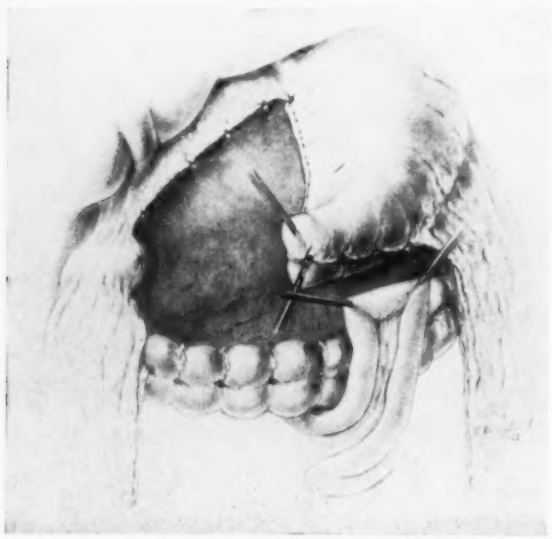

Fig. 12.

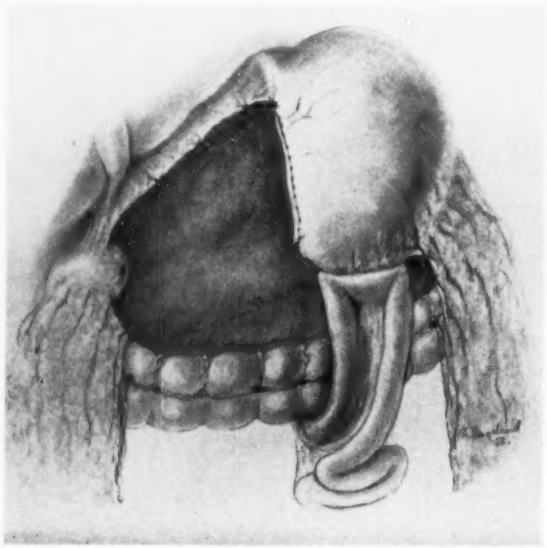

Fig. 13.

omentum and hepato-duodenal ligament reinforces the closure.

Following the double ligation of the left gastric artery and resection of the lesser curvature omentum to within one inch of the oesophagus a medium sized Payr clamp is applied to the stomach, as is shown in Fig. X. The lower portion is also clamped off by 12-inch crushing clamps and the stomach removed by cautery or knife. We prefer the cautery for bleeding vessels are sealed off by the cautery.

In the same manner as the duodenum was closed, the end of the stomach is closed. A #0 chromic catgut on an atraumatic suture is started and the first suture under the end of the Payr clamp is tied. Then always keeping the suture taut it is carried through until the greater curvature is reached. The Payr clamp is then removed and with the same suture the crushed edge is sutured through and through without locking until the lesser curvature is reached. This suture is tied to the same suture that started the closure. Interrupted silk #00 suture is used after the lesser curvature end is purse-stringed and inverted. This is shown graphically in a small insert in Fig. X. The greater curvature tip is also purse-stringed by silk and inverted. This gives a 3-layer tight closure.

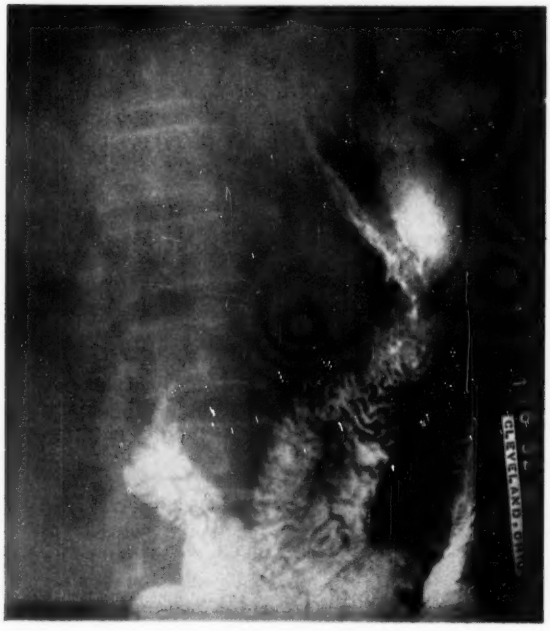

Fig. 14.

At this time it is necessary for the surgeon to decide whether to perform a retrocolic gastric resection or anticolic gastric resection.

If retrocolic gastric resection is chosen one follows the technique described for retrocolic gastrojejunostomy. The avascular space to the left of the middle colic artery is selected for anastomosing the short loop of the jejunum to the greater curvature of the stomach making an opening about 1¼ to 2½ inches long, as shown in Fig. XI. Following the technique described in Part I the completed anastomosis is shown in Fig. IV.

The colon mesentery is attached to the resected stomach below by interrupted silk sutures, as shown in Fig. IV, so there will be no possible way to have a hernia in any unclosed area, thereby causing obstruction.

If it is necessary to do a radical resection, such as the removal of 4/5 of the stomach, the anticolic anastomosis may be used. This is done by excising the omentum, bringing the jejunum of proper length over the top of the colon, and attaching the same as described in Part I of this article. This is shown in Fig. XII and Fig. XIII.

Patients operated on with this technique rarely vomit and rapidly are able to take fluids and food early in their convalescence.

Fig. XIV shows an actual x-ray plate of a post-operative high gastric resection for cancer of the stomach with 4/5 gastric resection with anticolic anastomosis. The patient made an uneventful recovery.

CONCLUSION

1. The principles applied in gastroenterostomy may be applied to a simplified gastric resection.

2. The simple gastroenterostomy anastomosis makes gastric surgery a safe procedure for it is necessary for one to learn only one simplified procedure.

3. Repeated performance of one simple standard procedure makes for perfection of technique and fewer complications, resulting in a very low morbidity and mortality.

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CLINICAL STUDIES IN BLOOD LIPID METABOLISM. VIII. DISTURBED SERUM LIPID PARTITIONS IN LIVER DISEASES WITH AND WITHOUT JAUNDICE.*

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THE LIVER is the master organ in the body and is concerned with the regulation and preservation of all the complex chemical and physical relationships of the physiology of life. Since the functions of the liver are many and varied, it is impossible to discuss all of them. Indeed, a recent survey of the literature enumerated ninety-seven listed liver function tests (1). The authors will confine themselves to the abnormal liver function causing disturbed serum lipid partitions in some liver diseases with and without jaundice.

Methods of Study

Hospitalized patients under investigation were suffering from some liver disease such as cirrhosis with and without jaundice; infectious hepatitis, and malignancy of the liver with jaundice. Age and sex varied. Fasting non-oxalated blood, 15 cc., was obtained and the serum was utilized. Duplicate samples of the serum were analyzed. The lipid phosphorus (lipid esters of phosphoric acid) were determined by the Youngburg modified digestive method (2). Phospholipid values were obtained by multiplying the lipid phosphorus determinations by the factor 25. Total lipids were determined by the gravimetric modified Bloor method (3). Total cholesterol and esters were determined by the Leiboff method (4). In order to express the value of cholesterol esters in terms of actual weight, a factor of 1.67 was utilized. This figure was obtained by dividing the molecular weight of cholesterol oleate by the molecular weight of cholesterol. Neutral fats were obtained indirectly by subtracting from the total lipid values the weights of the phospholipids, free cholesterol, and cholesterol oleate fractions. Lipid fraction percentages were calculated by dividing the weights of the various lipid fractions by the total lipids. Liver function methods performed were those of the thymol turbidity test by Maclagan (5); cephalin-cholesterol flocculation test by Hanger (6); and the total protein, albumin and globulin values by the Tyrosine method of Greenberg (7). Sedimentation values were performed by the Westergren method (8). Height, weight and type of constitution were noted. Definitions, functions of the lipid partitions, and detailed explanations of the methods were discussed in a previous publication (9).

Results

Non-jaundiced cirrhotic liver: Lipid changes in cirrhosis of the liver must be differentiated whether jaundice is present or not. In non-jaundiced cirrhotic livers, there was a slight increase of the lipid partitions both quantitatively and by percentage values. The arithmetical mean values of the lipid fractions were slightly above normal except neutral fats (Table I and fig. 1, #3). Lipid fraction percentage showed a slightly decreased neutral fat and increased phospholipid and esterified cholesterol Table I and fig. 2). This further corroborates observations of others that pathological fatty changes may not be reflected in disturbed chemical lipid determinations.

Jaundiced cirrhotic liver: The phospholipid values obtained were 3½ times; the total lipids and neutral fats twice; and the total cholesterol 1½ times normal values (Table I and fig. 1, No. 4). While the total cholesterol was increased, the partitions varied: the percentage of ester being less while that of free cholesterol higher than normal (Table I). Lipid fraction percentage values alone may be misleading, as the only findings are diminished esterfied cholesterol and increased phospholipids (Table I and fig. 2). What causes the increased phospholipids and total lipids with no comparatively corresponding disturbance of the total cholesterol values which are only one and one-half times normal? The histogram (fig. 1, No. 4) shows the highest values of lipid partitions for this condition. The increased phospholipids are made by the liver and are the carrying agent of the fats. The liver therefore must produce increased phospholipids in order to take care of the increased neutral fats (Table I) which must be transported through the system for further metabolism.

There is an overproduction of the phospholipids by the liver rather than a piling up due to biliary obstruction or decreased breakdown of the phospholipid molecules by the tissue. This has been found to be true no matter what the cause of the hyperlipemia in all the pathological states studied (10). However, with the disturbance in liver function as evidenced by jaundice, it is hoped to explain what jaundice with increased retention of bile and bile salts does with lipid values.

Non-jaundiced malignant liver: It is of interest to note that maligancy of the liver with no jaundice produces no increased total lipids. On the contrary, total lipids and neutral fats are diminished but the phospholipids are increased (Table I and figs. 1, 2). This may be seen in the percentage values (fig. 2) with the phospholipids and esterfied cholesterol increased and neutral fats decreased. Indeed, the percentage value of the neutral fats (27.8%) was lowest of the liver diseases (Table I). The neutral fats are markedly diminished compared to the increase of phospholipids. If one were to consider the cholesterol values with its subdivisions, one would think that the liver was not so completely disturbed. The cholesterol ester value is below normal if there should be very marked liver damage function, since esterification takes place

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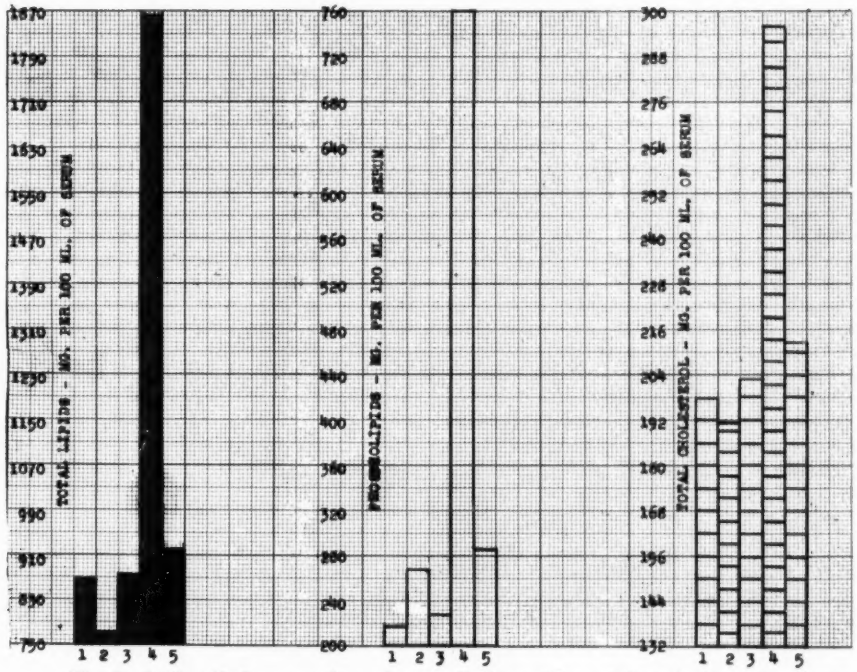

Fig. 1: Arithmetical mean values of serum lipid partitions of hepatic diseased patients. (1) Normal; (2) Malignancy without jaundice; (3) Cirrhosis without jaundice; (4) Cirrhosis with jaundice; (5) Infectious hepatitis with jaundice.

in the liver. It is noted that the values of ester and free cholesterol correspond to the normal percentages of total cholesterol (Table I). The decrease in total lipids and neutral fats in non-jaundiced malignant involvement of the liver is the pertinent finding requiring an explanation.

Infectious hepatitis with jaundice: There is an increase in all the lipid partitions except cholesterol esters, but not as marked as that of jaundiced cirrhotic patients (Table I and figs. 1, 5). The predominantly increased percentage partitions is that of phospholipids (Table 1 and fig. 2). The ratio of free to total cholesterol is slightly elevated. The authors have not observed a markedly increased neutral fat and diminished ester component as published by others. The increased total lipid value is due evidently to the increased phospholipids (fig. 1). The lipid fraction percentage actually reveals an increase of the free cholesterol and phospholipid (Table I). The neutral fat percentage values are less than normal. The hyperlipemia may resemble that of biliary obstruction but of less magnitude.

DISCUSSION

Since the functions of the liver are varied and numerous, the discussion will be confined to that

TABLE I.

ARITHMETICAL MEAN VALUES OF SERUM LIPID PARTITIONS IN HEPATIC DISEASED PATIENTS. VALUES EXPRESSED AS MILLIGRAMS PER 100 ML. SERUM AND PERCENTAGES IN TERMS OF TOTAL LIPID VALUES

Arithmetical mean of	Total Lipids	Lipid Phosphorus	Phospholipids	Cholesterol: Total	Cholesterol: Ester	Cholesterol: % of Total	Cholesterol: Esterified	Cholesterol: Free	Cholesterol: % of Total	Neutral Fats	Ratio of: Phospholipids to Cholesterol	Ratio of: Cholesterol to Phospholipids	Lipid Fraction %: Free	Lipid Fraction %: Esterified	Lipid Fraction %: Phospholipids	Lipid Fraction %: Neutral Fats
Normals	861	8.6	218	197	121	61.2	202	76	38.8	365	1.10	0.90	9.1	23.5	25.3	42.1
Cirrhosis without jaundice	873	9.1	228	203	127	62.0	211	76	38.0	360	1.12	0.90	9.2	24.8	26.6	39.4
Cirrhosis with jaundice	1868	30.4	760	296	148	50.0	244	148	50.0	716	2.56	0.39	8.1	13.0	40.6	38.3
Infectious hepatitis with jaundice	921	11.4	286	212	128	60.4	163	84	39.6	386	1.60	0.68	10.0	17.8	31.4	40.8
Cancer of the liver without jaundice	771	10.7	268	191	120	62.7	200	71	37.3	261	1.43	0.70	8.6	27.5	36.1	27.8

region which concerns the hepatic dysfunction, with and without jaundice upon disturbed serum lipid metabolism. We shall briefly consider the role of the liver in fat metabolism, especially its correlation with bile and its constituents; cholesterol and its partitions; phospholipids, and neutral fats. Above all the serum lipid partitions in the absence and presence of jaundice in some liver diseases and the etiological factor for the same will be discussed.

Function of the liver in fat metabolism: The liver plays an important part in the metabolism of fat as is evident by the following facts: 1) The liver extensively desaturates fatty acids (11). 2) Neutral fat or cholesterol esters may accumulate more in the liver than in any other tissue. 3) Ketogenesis occurs chiefly in the liver as a result of the oxidation of fatty acids and is the chief site of formation of ketone bodies (12). 4) The rate of phospholipid turnover in the liver is more rapid than in any other tissue with a possible exception of the intestinal mucosa during fat absorption. 5) The liver appears to act as a sorting point for fatty acids and a great central laboratory in which phospholipids for the tissues are assembled (13). 6) With respect to steroids the liver exercises three functions: a. the excretion of cholesterol in the bile; b. the formation and excretion of cholic acid; c. the destruction or inactivation by conjugation of steroid sex hormones. 7) The liver esterifies, synthesizes, stores and destroys cholesterol (14).

Normally, the liver does not store fat. The fats are brought to it as neutral fat, glycerides, fatty acids, and cholesterol esters and are oxidized there. The occurrence of cholesterol closely parallels that of fat and is indispensable for fat metabolism. Thus both fat and cholesterol are closely involved in liver chemistry. In the intestine cholesterol absorption occurs only in the event of simultaneous fat absorption. Free fat, fatty acids, cholesterol, and cholesterol esters are all absorbed by the same route, e. g., via the lacteals, into the lymphatics, into the thoracic duct and thence into the blood stream. The newly formed fatty acids are combined with cholesterol as esters, and are so released into the circulation. These fatty acids may be combined with phosphoric acid, glycerol, and choline to form a liver phospholipid—lecithin. If phospholipid synthesis is impaired, owing to a chronic deficiency of the vitamin-like lipotropic factors or to some other impediment in fat metabolism, fatty infiltration of the liver takes place. The liver discharges the phospholipids into the circulation.

Types of fatty liver: A fatty liver is characterized by the infiltration and deposition of excessive amounts of fat. The fat deposit is divided largely between neutral or glyceride fat and bound sterol fat in the form of cholesterol esters. Fatty livers differ in type essentially in the ratio of glyceride to sterol fat. Thus, in fatty livers resulting from high fat feeding, low protein diets, choline deficiency, or from thiamine or biotin imbalance, the pathological picture consists of a predominance of glyceride fat and a relatively small amount of cholesterol esters. In the fatty livers induced by an intake of excessive amounts of cholesterol, cholesterol and sterol esters may predominate over glycerides although Best et al (15) found that, even with intakes of cholesterol up to 1.5% of the diet, glyceride fats predominate over cholesterol in the resultant fatty liver.

Phospholipids: The liver is a main source of the plasma phospholipids. If the level is high, there is an overproduction of the phospholipids by the liver rather than a piling up due to biliary obstruction or decreased breakdown of the phospholipid molecules by the tissues. This has been found to be true no matter what the cause of the hyperlipemia in all pathological states studied (10). Animals on a diet free from phospholipids can produce their own choline. Therefore, choline is looked upon as the lipotropic agent par excellence. In the ordinary diet choline is present chiefly in the form of phospholipids. Since these are fat soluble substances they are plentiful in fats rich in cholesterol, such as eggs, brain, kidney, and liver.

A low fat diet, while it may be full of choline need not cause any deficiency of lipotropic factors provided it may be rich in animal proteins, since the latter supply an abundance of methionine, which the body can convert into choline. The importance of the phospholipids in the handling of fats is by no means limited to transport. In almost every instance of fat and sterol metabolism throughout the body, the phospholipids play a dominant role. Absorption of fats from the gut through the intestinal wall is closely tied up with phosphorylation and phospholipid formation. In the liver, the great chemical factory of the body, improper fat handling leading to fatty infiltration and cirrhosis, has been shown to be associated with faulty phospholipid formation.

Phospholipids play a role in the permeability of cell membrane, muscular activity, and in the function of the nervous system. Recent studies show that the plasma phospholipids do not only transport fatty acids from one tissue to another as many have believed (16). In the normal person the colloid stability of cholesterol is unchanged because the serum phospholipid rise is proportional to the serum cholesterol rise. There is a relationship between the absorption of fats and the metabolism of phospholipids in the intestinal mucosa (17). Phospholipids are formed in the intestine and liver (18). Phospholipids of the liver mitochondria might be the immediate precursor of the phospholipid in the plasma (19). The blood phospholipids are not the carriers of the fatty acid from the liver to the depots. Phospholipid formation is essential for the delivery of fatty acid residue from the intracellular to the extracellular compartment (20).

Cholesterol: (21, 22) Cholesterol is an essential constituent of all cells and fluids of the body. It is a precursor of cholic acid and cholestenone and also functions with the bile acids and salts in facilitating the absorption of fatty acids. It is an important means of transportation of fatty acids in the blood, through the formation of cholesterol esters. It is present in highest concentration in the adrenal cortex and its biological precursor of steroid hormones. It is an important source of vitamin D by irradiation of the skin, with the formation of activated 7-dehydrocholesterol. It may be involved in cell permeability and possibly in immunologic reactions.

The cholesterol in the body is derived from two sources, endogenous and exogenous. Endogenous cholesterol is synthesized in the liver, intestinal mucosa, skin, but not in the aorta (23). Exogenous and endogenous cholesterol are present in the intestine and react with the fatty acids. Some free cholesterol is trans-

formed into coprosterol and excreted through the feces. The esterified form is absorbed and is carried to the liver where the cholesterol in part is "liberated," the fatty acids entering into combinations with phosphoric acid and choline, which may be present within the lumen of the intestine to form lecithin. Some fatty acids give rise to acetates, considered to be the building blocks for cholesterol synthesis.

Cholesterol combines with fatty acids to form esters (25). The esterification of cholesterol changes its physical properties, which not only have an influence on the absorption and transportation of this substance in the tissue fluids but are also important for the composition of cell lipids. A cholesterol esterase also seems to be present throughout the body. The liver plays an important role in regulating the ratio of free cholesterol to cholesterol esters.

Cholesterol probably enters into complex molecular combination with protein in the parenchyma of the liver. Thus, there are released into the blood stream four varieties of cholesterol, derived fundamentally from either exogenous or endogenous cholesterol.

1) Synthesized (endogenous).
2) Originally ingested (exogenous) now nonesterified.
3) Giant molecular cholesterol-protein complex.
4) Esterified cholesterol (hepatic and intestinal).

Some of this cholesterol is returned to the liver to be secreted in the bile along with cholesterol which enters the bile directly from the liver. Thus, the circuit intestine-liver-blood stream-bile-intestine—the so-called entero-hepatic circulations—is complete.

Composition of bile: Bile is a product characteristic of the vertebrates' liver. Bile is secreted continuously by the liver cells. It passes along the bile capillaries, hepatic and cystic ducts to be stored in the gallbladder. Its expulsion from the latter and its passage along the common duct into the duodenum is intermittent, related in time to the arrival of food in the intestine, and is quite independent of the actual secretion by the liver.

TABLE II

SCHEMATIC COMPARATIVE SERUM LIPID CHANGES IN HEPATIC AND METABOLIC DISEASES, WITH AND WITHOUT JAUNDICE

State	Total Lipids	Cholesterol			Phospholipids	Neutral Fats
		Total	Esters	Free		
Malnutrition	D					
Fatty liver	D	D			D	
Starvation	I	I or D				
Non-jaundiced liver Cancer	D	N	N	N	I	D
Cirrhosis	N	N	I*	N	I*	D
Jaundiced liver Cirrhosis	I	I	D	I	I*	I
Infectious Hepatitis	I	I	D	I	I*	I

N—normal; D—decreased; I—increased; *—pronounced changes.

Composition of the human bile consists of water and salts. Of the latter may be mentioned mucin and pigments; bile salts; fatty acids from soap; cholesterol, lecithin, fat, and inorganic salts. The chief biliary components are the bile salts, bile pigments, cholesterol, and lecithin. As a result of the absorption of water and inorganic salts, gallbladder bile is several times more concentrated in organic solids than liver bile. Beside serving as a vehicle for the excretion of pigments and certain other waste products from the body, the bile performs important functions in the intestine. Bile is essential for the efficient digestion of fat by the pancreatic and intestinal juices, due to its bile salts. Bile is of much greater importance for fat absorption than for fat digestion. Bile is necessary for the absorption of Vitamin D, apparently due to its bile salts (26).

Bile salt metabolism: The parent substance from which bile acids and the corresponding bile salts are produced is as yet unknown, but it is established that the liver is responsible for their synthesis and for their secretion. Bile salt synthesis by the liver is a complex process which is capable of being influenced qualitatively and quantitatively by many factors. The maintenance of a continuous circulation of bile salts between the intestines and the biliary system is a necessary factor in the preservation of normal hepatic physiology. Retention of or a deficiency of bile salts may, in turn produce secondary damage to the liver.

Function of bile salts: The function of the bile salts is as varied as the factors influencing their synthesis, secretion, and excretion. A major function of the bile salts is that of controlling the digestion and absorption of the lipids. Bile is a necessary factor in the emulsification, digestion, and absorption of fat. The activity of bile in these respects depends upon its bile salt content.

Cholesterol absorption as well as that of neutral fat is dependent upon the bile in the intestines since the uptake of steroids from the intestinal tract is apparently dependent upon a simultaneous absorption of fatty acids.

Bile acid metabolism: The bile acids, glycocholic and taurocholic acids, are present in the bile and blood as their sodium salts, the relative proportions of the two substances varying in different individuals. Isotope studies have shown that cholic acid can be formed in the organism from cholesterol, and the latter from acetate, indicating an intimate metabolic relationship between bile acids, cholesterol and fatty acids. In the liver, cholic acid is conjugated with glycine and taurine (from cystine) to form glycocholic and taurocholic acids. There is considerable evidence of an indirect nature suggesting that the bile acids are formed in the liver. Following their elimination in the bile they are absorbed from the intestine and returned to the liver in the portal circulation. This cycle has been termed the enterohepatic circulation of bile acids. The liver appears to destroy about half of the bile salts which it forms daily (27).

Pigment metabolism: Bilirubin, the chief pigment of human bile, is derived from hemoglobin by a process of

hydrolysis. It has been rather definitely established that the cells of the reticulo-endothelial system, especially those present in the bone marrow, spleen and liver (Kupffer cells), are concerned with the metabolism and formation of bile pigment. Although the hypothesis that the hepatic polygonal cells may play a part in the formation of bilirubin has not been entirely abandoned, it is generally agreed that their chief function in this connection is the removal of bilirubin from the blood stream and its excretion in the bile. In the upper intestine, bilirubin is reduced successively to mesobilirubin, urobilinogen (mesobilirubinogen) and stercobilinogen by the action of putrefying bacteria. A fraction of the urobilinogen is reabsorbed into the portal circulation and is carried to the liver (enterohepatic circulation); the major portion of this fraction is removed from the portal blood by the hepatic cells and is perhaps reconverted into bilirubin or a hypothetical pigment complex, the remainder escaping into the general circulation to be excreted in the urine (0-4 mg. daily). The portion which escapes reabsorption from the intestine is oxidized to urobilin, mesobiliviolin and stercobilin, which are the normal pigments of the feces (40-280 mg. daily, usually 100-250 mg.). There is some question as to whether any bilirubin is absorbed from the intestine; none is present normally in the feces of adults (28).

Jaundice: When bile pigment is present in excessive amount in the blood (hyperbilirubinemia) it diffuses from the capillaries. The skin, mucous membranes, and conjunctivae then become stained a pale yellow tint. The discoloration is called jaundice or icterus. Jaundice may be due to the production of bile pigment in excess of the amount with which the excretory power of the liver can cope. On the other hand, it may result from the failure of a damaged liver to excrete the bilirubin produced in normal amounts (29).

A consideration of the pathogenesis of the various possible types of hyperbilirubinemia leads to the classification of jaundice into that of hemolytic, obstructive, or hepatocellular types.

It is not the purpose of the authors to discuss in detail the differential diagnosis of jaundice by varied laboratory procedures nor types. Our interest lies in the explanation for the lipid partition disturbance encountered in hepatic diseases with and without jaundice.

The presence of jaundice, increased cholesterol, and phospholipids has definitely been shown to be present in both obstructive and non-obstructive conditions. The primary hepatic involvement such as hepatitis, due to chemicals or virus infections may produce a state simulating that caused by extrahepatic obstruction (30, 31). At times it may be impossible clinically to differentiate the underlying etiological disturbance. Ahrens and his associates (32) in an elaborate study speak of a primary and secondary biliary cirrhosis, depending upon the level of lipid disturbance and the presence of xanthomatous lesions. Shay and his co-workers (33) correctly doubt such a clear cut picture. They speak of a "hepatocellular hypercholesterolemic cirrhosis" for the pericholangiolitic biliary cirrhosis. This group is produced by hepatotoxic agents whether recognized or not. A secondary variety in which the clinical and serum lipid pictures may be indistinguishable from the above groups may be found in those patients in whom extrahepatic biliary obstruction initiated the disturbance. This is considered a primary biliary cirrhosis.

Friedman and his associates (34) believe the hypercholesteremia of rats after biliary obstruction to come from the liver and to be due to an accumulation of bile acid, especially cholic acid in the plasma. It was not due to any failure in either the biliary or intestinal excretion of cholesterol nor by any mechanical or nervous reaction arising from the mere distention of biliary duct produced by bile duct ligation (35). Contrary to others they believe (36) that bile duct cholesterol was intermittently related to the synthesis or turnover of hepatic cholesterol. Bile acid represents an increment of that cholesterol synthesized in the hepatic cell itself. The hypercholesteremia in jaundiced patients is not due to inadequate intestinal excretion of cholesterol. The above authors assert that the accumulation of bile acids after biliary obstruction is sufficient in itself to initiate the process responsible for the hypercholesteremia. They determined serum cholesterol and cholate values in a group of patients and concluded that clinical hypercholesteremia may be a phenomenon secondary to initial derangement of cholate metabolism. This implies the importance of the liver when evaluating factors involved in the pathogenesis of hypercholesteremia in man(37). The authors (38) have previously maintained that the liver may be the single organ for a common metabolic denominator for abdominal lipid metabolism.

SUMMARY

The determinations of cholesterol and phospholipid partitions alone are not sufficient to represent a state of hyperlipemia, since these fractions may be subnormal in such conditions (39, 40). As stated in previous publications, one must determine all the lipid partitions to evaluate true disturbances in lipid metabolism (9, 41, 42).

Lipid fractions such as cholesterol with its partitions, lipid phosphorus, neutral fats and total lipids were determined in a group of patients afflicted with liver disease. The conditions were those of malignancy of the liver without jaundice, cirrhosis with and without jaundice, and infectious hepatitis with jaundice.

In the non-jaundiced malignant livers, the total lipid values and neutral fats were diminished while the phospholipids were slightly increased. The cholesterol and its subdivisions were within normal range. Decreased neutral fats, liver destruction and malnutrition are factors predisposing to the hypolipemia encountered in this group of patients. It is well known that a hypolipemia may occur where destruction of the liver substance is so advanced that the metabolism of lipids by the liver is hopelessly compromised. Malnutrition, which in itself gives rise to hypolipemia (fig. 2) may also be a contributory factor. The effect of impaired absorption for utilization of lipids or essential dietary factors cannot be neglected in evaluating the distorted serum lipid patterns. In spite of the hypolipemia, the phospholipids were increased showing the effect of the human body to attain some equilibrium so that the available fats may be transported where needed.

In cirrhosis without jaundice, it is interesting to note

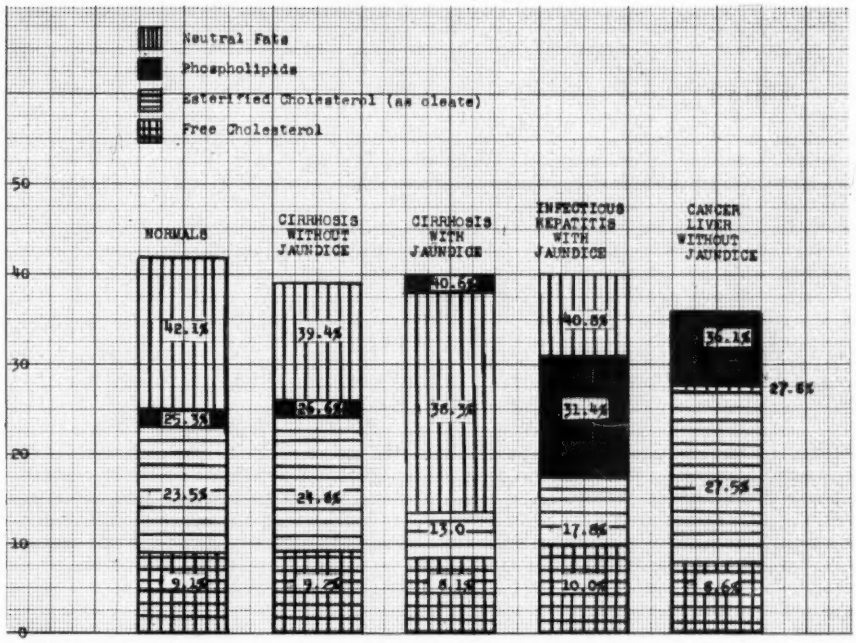

Fig. 2: Graphic representation of arithmetical mean of serum lipid pattern in hepatic diseased patients. Percentages are in terms of total lipid values.

that the serum lipid partitions were practically within normal range or very slightly increased. The esterified cholesterol and phospholipids were slightly increased. The chemical determinations of lipid partitions do not reflect the underlying pathology that may be present in non-jaundiced cirrhotic livers; namely: fatty infiltration or degeneration. These findings concur with the hypolipemia associated in the dietary fatty livers (43). Severe injury to liver parenchyma from any cause appears to invite fatty infiltration of this organ and disturbances of serum lipids resembling those of dietary fatty livers. The cholesterol and phospholipids may be reduced with undue proportion of phospholipids in the liver. Dietary deficiencies of lipotropic substances and animal proteins cause fatty liver and cirrhosis in animals under certain conditions. Fat accumulates in large amounts due to defective phospholipid synthesis by the liver. Fat is transported in the blood and partly at least as phospholipids and as esters of cholesterol which are produced mainly by the liver. Hence, we encounter an increased value for esterified cholesterol and phospholipids with a normal total lipid value in non-jaundiced cirrhotic liver.

In jaundiced cirrhotic livers on the other hand, we note a different picture for the serum lipid partitions. It seems that the highest values for the lipid fractions are found in this group of liver cases. All lipid components were increased except the esterified cholesterol. It must be noted however that comparatively the phospholipid fractions increase more than the others. Indeed, the increased phospholipid values were threefold compared to those of the increased total cholesterol. As mentioned above the increased phospholipids are essential to carry the load of the extra neutral fats available.

In the case of infectious hepatitis with jaundice all the lipid partitions are increased except the esterified cholesterol as observed in patients with jaundiced cirrhotic livers. However, the lipid values are not so high. This is the group of jaundiced cases due to intrahepatic inflammatory disease producing lipemia simulating extrahepatic blockage. Studies of viral hepatitis have shown these varied pathological processes to explain laboratory data similar to those noted in extrahepatic obstruction.

Without a doubt one cannot deny that the hyperlipemia in the above jaundiced patients studied was correlated directly with the icterus and hyperbilirubinemia. This may be explained by the accepted fact that bile, especially its bile salts, is a necessary factor in the emulsification, digestion, and absorption of fats. Retention of or deficiency of bile salts produces secondary damage to the liver. It has recently been shown that the hypercholesteremia in jaundiced patients need not be due to any failure in either the biliary or intestinal excretion of cholesterol as has always been accepted to date. Derangement of cholate metabolism is shown to be a factor in producing hypercholesteremia in jaundiced patients.

CONCLUSIONS

1) Serum lipid fractions as total cholesterol, esterified and free cholesterol, phospholipids, neutral fats, and total lipids were determined in hepatic diseases with and without jaundice.

2) Hypolipemia encountered in non-jaundiced malignant livers is thought to be the result of decreased neutral fats, liver destruction and malnutrition.

3) Cirrhotic livers without jaundice presented a practically normal serum total lipid values with increased phospholipids and esterified cholesterol fractions.

4) The serum lipid partitions observed in non-jaundiced cirrhotic livers may simulate the hypolipemia of dietary fatty livers.

5) Chemical serum lipid partitions may not reflect the underlying liver pathology or fatty changes.

6) Hyperlipemia in jaundiced (infectious or viral) hepatitis may simulate those in extrahepatic blockage.

7) Hyperlipemia encountered in jaundiced (hyperbilirubinemia) conditions whether due to intra or extrahepatic disturbances need not be due to failure in biliary or intestinal excretion of cholesterol nor by duct distention.

8) Hyperlipemia obtained in jaundiced patients may be due to the accumulation of bile acids and especially a derangement of cholate metabolism in the blood.

9) The liver must be considered when evaluating factors involved in the pathogenesis of hypercholesteremia.

10) All serum lipid fractions must be determined to evaluate a true disturbance in lipid metabolism.

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ABSTRACTS ON NUTRITION

GARLAND, H. AND TAVERNER, D.: *Diabetic myelopathy.* Brit. Med. J., June 27, 1953, 1405-1408.

The authors call attention to a form of diabetic neuropathy previously described by Bruns in 1890 but forgotten. The syndrome consists of asymmetrical pain, weakness, muscle-wasting, and loss of reflexes in the legs, without objective sensory disturbance, in middle-aged patients with diabetes of relatively short duration. The protein content of the cerebrospinal fluid usually is raised. The plantar responses often are extensor and the electromyographic changes in the affected muscles are compatible with a myelopathic lesion. Five new examples are described. Recovery takes place after proper treatment of the diabetes.

HIRSON, C., FEINMANN, E. L. AND WADE, H. J.: *Diabetic neuropathy.* Brit. Med. J., June 27, 1953, 1408-1413.

About half of all cases of diabetes show neurological disease. One form is rapidly relieved by proper diabetic treatment. In 3 percent of cases there is a form unrelated to diabetes which goes by remissions and relapses. Finally, there is a form which is chronic, permanent and not disabling. There is no evidence that arteriosclerosis of thiamine deficiency is a causal agent. The glucose-tolerance test should be employed in cases of obscure neurological disease.

DAVIS, J. W.: *Hypervitaminosis D due to Ertron.* Texas State J. M., 49, 7, July 1953, 524.

Davis reports the case of a 57 year old widow who had taken 3 capsules of Ertron daily for 8 months because of arthritis. Her B. P. was 220/100. The serum calcium was 17 mg. percent. Two large renal calculi were found in the right kidney. After stopping the vitamin D she improved considerably in one week and was able to go home, but the serum calcium was still high—15 mg. percent. Her complaints had included fatigue, loss of weight, fullness in the epigastrium and frequent nocturia.

TUTTLE, W. W., DAUM, K., ROBERTS, H. AND RANDALL, B.: *Physiological response to size and content of breakfast by men over 60.* J. Am. Dietetic Assn., 29, 1, Jan. 1953, 34-40.

It was found in men over 60 that a basic cereal-and-milk breakfast and a basic bacon-egg-and-milk diet breakfast of equal protein content and caloric value were equally effective in promoting mental and physical efficiency in the late morning hours. Such breakfasts are better than a heavy breakfast consisting of ordinary breakfast items for this purpose.

KOTKOV, B.: *Experiences in group psychotherapy with the obese.* Psychosomatic Med., XV, 3, May-June 1953, 243-251.

Group psychotherapy for ages 20 to 40 served as a valuable relationship experience for the *maintenance* of weight loss in 48 percent of the patients who did not succeed by other methods. However, no amazing over-all weight loss occurred.

ASHBY, D. W. AND TWEEDY, P. S.: *Friedreich's ataxia combined with diabetes mellitus in sisters.* Brit. Med. J., June 27, 1953, 1418-1421.

The authors describe the 11th instance on record of Friedreich's ataxia occurring in combination with diabetes in siblings. The former disease precedes the latter. While the occurrence of the two diseases in one person may be coincidental, the occurrence of both in siblings suggests either an hereditary syndrome or an effect determined by the genetic *milieu* of the ataxia-bearing gene.

TUTTLE, W. W., DAUM, K., IMIG, C. J., RANDALL, B. AND SCHUMACHER, M. T.: *Effect of omitting breakfast on the physiological response of the aged.* J. Am. Dietetic Assn., 28, 2, Feb. 1952, 117-123.

Omitting breakfast, in older men, did not affect the choice reaction time, but there was usually increased muscular tremor, and the maximum grip strength was decreased. Dyspnea was also noted in half the cases.

FOX, J. R.: *Thirty-two cases of renal glycosuria.* Journal-Lancet, July 1953, 275-277.

Thirty-eight cases of persistent recurrent glycosuria on a non-diabetic basis were found among 19,358 patients examined. Fasting blood sugars were within normal range. There were 2 types of glucose tolerance curves found,—(1) the normal curve with the peak generally under 150, but with sugar in the urine; (2) a high peak curve with the upper reading over 180. There was a return to normal or hypoglycemic state within 2½ hours, and glycosuria appeared. One must rely on an abnormal fasting blood sugar or on abnormal glucose tolerance test in making a diagnosis of diabetes before starting treatment.

ALEXANDER, R. I.: *Fatal hypoglycemia in a diabetic patient with pituitary necrosis.* Brit. Med. J., June 27, 1953, 1416-1418.

A patient with diabetes who had been many hours in *hypoglycemic* coma eventually died, and post-mortem showed necrosis of the pituitary gland. Presumably the Houssay phenomenon had been partly duplicated here, especially since, during his fatal illness, the patient had become excessively sensitive to insulin. It is known that 3 hours of hypoglycemia coma is compatible with recovery, but the present patient had been in such coma for 11 hours before admission, and then remained in coma despite the rise of blood sugar from infusion. His death was due to prolonged hypoglycemia, and this, in turn, seemed to be caused by pituitary necrosis, a condition which may occur in diabetes. One lesson to be learned from the case is that in brain sugar there is a low point of "no return," provided it continues much more than 3 hours.

LAWSON, D. F., DEGARIS, C. N. AND BOLTON, J. H.: *Folic acid and reproductory efficiency.* Med. J. Australia, June 13, 1953, 848-849.

A lymphocyte count of less than 1500 per cubic millimeter is regarded as evidence of folic acid deficiency. 77 such obstetrical cases were found. All had had poor obstetrical histories,—miscarriages, unexplained stillbirths, unexplained premature births or full term infants weighing less than 6 pounds. Correction of the folic acid deficiency produced marked improvement in the reproductory efficiency. High protein and vitamin intake and maintenance of normal hemoglobin levels also are of importance.

EDITORIALS

IRRITABLE COLON AND THE SMOOTH DIET

There is a noticeable tendency, in the past few years, to permit patients with symptom-producing spastic colons to partake of "normal" diets, rather than to restrict the cellulose-containing foods. There are several aspects of this problem which require comment.

When a patient is told to eat what he desires, a psychological advantage obviously is gained, inasmuch as the patient feels assured that his condition cannot be as serious as he had imagined. He is furthermore relieved of the necessity of constantly studying his food, and—so far as it goes—this directs his attention away from his abdomen. Most will agree that a normal or customary diet will be somewhat better for the patient, particularly from the vitamin standpoint. Finally, the "addiction" of Americans to the use of salads made of fresh vegetables and fruits has become deep-rooted, so that the foregoing of salads and fresh foods generally runs counter to the cultivated taste of the individual, and he actually suffers, mentally at least, from their lack.

In practice, it is true that not a few persons with mucous colitis will do better, on the whole, if they are permitted to eat what they wish. In such cases the general nutrition and sense of well-being are noticeably better than in those for whom a strictly smooth diet is enforced. Actually, when *any* kind of special diet is prescribed for anyone, there is a general tendency toward weight loss, due, undoubtedly, to the fact that the individual loses some of his appetite.

However, clinical acumen is required in permitting the liberty of a normal diet in cases of spastic colon. Experience shows that in persons under unusual strain, or in those in whom colonic spasm and pain have become habitual, every means of bringing comfort should be used, and the low-roughage diet is one good means. When improvement occurs, a gradual resumption of more and more of the normal foods should be tried out. The test is the eating. If the patient can eat roughage without distress, that is the answer. But there will remain the group of persons who can *never* eat much roughage, and in these cases vitamin supplementation is highly important, particularly ascorbic acid. Of equal importance, from the standpoint of comfort is the continued use of small doses of sedative and belladonna. It goes, without saying, that a sympathetic understanding of the nervous influences present, does much in the way of successful psychotherapy.

CANCER EXCERPTS

Woedeman, with an able group of editors, has now added "Cancer" to the existing 15 sections of Excerpta Medica. The first volume does credit to the editors. Brief but informative abstracts on every phase of this broad subject are presented in a 100-page edition. In 1953 the cost is $5.00 for 6 volumes. In 1954, a monthly volume will appear, the price being $10.00 per year. The address of *Excerpta Medica* is 111 Kalverstraat, Amsterdam, C, Holland. We recommend "Cancer" very highly.

BOOK REVIEWS

LES VOIES BILIAIRES. Guy Albot, G. F. Bonnet, M. Champeaux, M. Chiray, Ch. Debray, R. Dupuy, R. A. Guttman, J. Hepp, Cl. Houdard, Cl. Olivier, F. Poilleux and J. Toulet. Masson and Co., Paris, 1953, 2.290 fr.

This splendid volume of 290 pages contains 161 illustrations. Diseases of the biliary system are individually outlined, then follow case reports. Albot and Poilleux organized this plan of teaching at the Hotel Dieux. Each discussion is contributed by two or sometimes three physicians, surgeons or radiologists, so that both the theoretical and practical aspects of each topic are well covered, and by authorities in each field. The volume should be published in English.

THE BOOK OF HEALTH. R. Lee Clark, Jr., M. D. and Russell W. Cumley, Ph. D., Elsevier Press, Inc., 1953. 155 E. 82nd St., New York, $10.00.

A volume of 800 pages with 1400 illustrations selling at $10.00 is somewhat unusual. The authors are thoroughly qualified. The advisory board and the editorial board contain the names of several hundred physicians, almost all of whom are at the top of the medical profession. The book obviously is written for the public. It describes the development of the body and the diseases which afflict it, and appears to cover this vast subject in an acceptable manner, so that it represents the present body of medical knowledge. The unusual volume may be recommended without reservation to anyone desiring to form a more accurate knowledge of medicine. We would predict a wide popular sale of the book. Its wide acceptance by the public would make the physician's task easier by inculcating accurate, as opposed to inaccurate, concepts of health and disease.

DISEASES OF THE LIVER, GALLBLADDER AND BILE DUCTS. S. S. Lichtman. Third edition. Two volumes, 1315 pages and complete index in both volumes. 220 illustrations, 3 plates in color. Lea & Febiger, Philadelphia, 1953. Per set: $22.00.

S. S. Lichtman's well known book "Diseases of the liver, gallbladder and bile ducts" is now published in the third edition. The new edition was necessary, as much new work has been done during the past few years. Many workers attempted to find the correlation between structure and function of the liver. Progress has been made in chemical and electrophoretic fractionation of the serum proteins. Punch biopsies have become more and more popular, though many risks are involved in this examination. The etiology of liver disease and the role played by virus infections is fully accepted. The part played by still undefined nutritional deficiencies constitutes an important, unexplored field. Lipotropic deficiency is now more clearly circumscribed and its therapy seems to be limited to the early stages of choline and protein deficiency states. Cortisone and ACTH have proven disappointing as effective agents in liver disease. The dietary factor continues to play an important part in therapy.

All these questions and many more are discussed by Lichtman, for he has a tremendous experience in this field. The basis is the new findings in the anatomy based on H. Elias' findings. Every reader will benefit from his suggestions in new advances in infectious hepatitis and portal cirrhosis. A very welcome addition is the enlarged chapter on symptoms and signs of liver disease and the entirely revised chapter on hepatic coma. The discussion regarding the mechanisms producing ascites is very interesting.

We enjoyed seeing Lichtman's experience with liver biopsies and the author's recommendations of extreme caution in its use. The findings of this examination are discussed. Of course, of greatest importance are his discussions of the many liver tests, to which he devotes 100 pages of the book. The different techniques are presented and the evaluation of the tests thoroughly discussed. The new and important advances in the section on gallbladder and the bile ducts are dealt with extensively.

A great improvement is found in the fact that the work is published in two handy volumes. Each part has a very thoroughly integrated and useful index. The references, placed at the end of each chapter, are extremely extensive. The many illustrations, as well as the printing, are of the best quality. This is indeed a fundamental book on liver, gallbladder and bile ducts, giving every available reference to all work done here and abroad. It is to be highly recommended to general practitioners, specialists in gastroenterology and surgeons who would be interested in the surgical aspects. We are happy to congratulate Dr. Lichtman on this outstanding work.

Franz J. Lust.

CLINICAL PHYSIOPATHOLOGY OF ACHLORHYDRIA AND HYPOCHLORHYDRIA. G. Dominici and D. Furbetta. Edizioni Scientifiche Italiane, Napoli, Italy, 1953.

Obviously the authors have produced a careful and exhaustive study of anacidity, which will prove particularly valuable to those capable of reading Italian.

THE BRITISH ENCYCLOPAEDIA OF MEDICAL PRACTICE. Edited by Lord Horder. Butterworth & Co., Ltd., Bell Yard, Temple Bar, London, England, 1953.

The term "encyclopaedia" seems inapplicable to this annual volume, because it is actually a "year book," although in a special sense. Progress in all fields of medicine during the past year are admirably described and condensed, so that it is well worth any physician's time to read it carefully. Abstracts arranged alphabetically according to subject comprise about one-half of the volume. There is something blunt and direct about British medical authors that should be more widely emulated in this country.

GENERAL ABSTRACTS OF CURRENT LITERATURE

GIANTURCO, C. AND MILLER, G. A.: *Routine search for colonic polyps by high-voltage radiography.* Radiology, 60, 4, April 1953, 496-499.

The essential point of this paper is that polyps which may be unnoticed in the barium filled colon, may become visible by using high voltage, e.g. 120 or 130 k. v. instead of the usual lower voltages. High voltage radiographs may be expected to detect polyps in 2 per cent of adult patients. This has an important and obvious bearing on the problem of cancer detection and cure.

POTTER, R. M.: *Dilute contrast media in diagnosis of the colon.* Radiology, 60, 4, April 1953, 500-504.

Potter finds that there is a better chance of detecting colonic lesion by using a more dilute barium suspension than usually is employed. About 4.5 ounces of barium sulfate to a quart of water with suitable suspending agents is suggested. He also suggests using high-kilovoltage radiographic technic, e.g. 85 to 100 k.v., as a second means of rendering visible small lesions which would escape detection under routine methods.

OWEN, J. G.: *The surgical significance of satellite polyps in cancer of the colon.* Bull. Mason Clin., 7, 1, March 1953, 23-29.

The mucosa of the colon, especially the rectum and sigmoid, shows marked potentialities for malignancy by its frequent growth of adenomatous or carcinomatous polyps. In cancer of the colon, care must be taken to rule out or locate satellite or multiple lesions, which occur in about one-third of the cases. Polyps of the colon should be treated by total removal for frozen section, and by segmental bowel resection if proved malignant. Malignant changes occur in about 20 percent of satellite polyps.

SNOW, D. J. R.: *Infective hepatitis among student nurses: an epidemiological study.* Med. J. Australia, Mar. 21, 1953, 406-409.

Infectious hepatitis is a disease which nurses may easily acquire, and it may also cause cross infections among hospital patients. In the Princess Margaret Hospital for Children, at Subiaco in Western Australia, following the admission of 3 cases, no less than 29 nurses and one medical officer acquired the disease in the ensuing 13 months. The possible modes of spread include personal contact (droplet infection or fecal contamination), contamination of water with infected feces, and contamination of food by flies or food handlers. Yet it is uncertain just how the infection was transferred in the present series. The author suggests that infective hepatitis should be treated in recognized hospitals for infectious diseases, where special precautions are most likely to be observed.

SHAPIRO, R.: *A preliminary report on Teridax, a new cholecystographic medium.* Radiology, 60, 5, May 1953, 687-690.

Teridax (Schering) seems to overcome the shortcomings of both Priodax and Telepaque. In the former, side effects were rather pronounced. In the latter, the shadow of the gallbladder was so dense as to obscure stones, and since Telepaque is excreted by the bowel, confusing shadows occurred. Teridax is excreted by the kidney and produces a shadow intermediate in density between those of Telepaque and Priodax. The extra-hepatic biliary ducts are frequently visualized by Teridax.

MARTIN, F. R. R. AND CARR, R. J.: *Crohn's disease involving the stomach: a report of two cases.* B. M. J., Mar. 28, 1953, 700-702.

The absence of mucosal folds in the antrum and in the duodenum, as seen in x-ray films, led to the suspicion of Crohn's disease in the stomach, and this was confirmed in one case by biopsy of the stomach, which showed that the stroma was heavily infiltrated by lymphocytes, plasma cells and endothelial cells. Giant cells were present but no caseation or tubercle bacilli were found. The diagnosis in the other case rested on x-ray evidence. Crohn has stated that vomiting and nausea are rare and occur only in the later stenotic phases of the disease. The authors think that Crohn did not envisage the disease in the stomach, and that where persisting anorexia and vomiting occur in Crohn's disease the possibility of gastric and duodenal involvement should be considered.

KARUSH, A. AND DANIELS, G.: *Ulcerative colitis: the psychoanalysis of two cases.* Psychosomatic Medicine, XV, 2, March-April 1953, 140-167.

This very careful and ably reported analysis of two cases of ulcerative colitis is chiefly valuable in that it demonstrates that the first attack of colitis began, in each case, within 3 to 4 weeks or sooner after a sudden, unforeseen threat to the "security of a previously elaborated self-esteem system." The article must be read in its entirety, but it constitutes one more contribution to the theory that ulcerative colitis is a psychogenic disease. (The usual argument in rebuttal is that everyone, whether subject to this disease or not, will be found, on careful psychological examination, to have passed through similar experiences. —Abstractor).

SANCHEZ, A. R. AND GONZALES, D. T.: *The simultaneous use of multiple antibiotics in combination in the treatment of peritonitis.* Antibiotics and Chemotherapy, 3, 3, March 1953, 223-227.

Ten cases (4 due to traumatic perforation of a hollow viscus; 4 due to ruptured appendix; 1 due to perforated gastric ulcer, and 1 due to a pyosalpinx complicating a tuberculous salpingo-oophoritis) of peri-

tonitis were all cured by the use of a preparation named "Estreptotracina," each vial of which contained 300,000 units of procaine penicillin G; 100,000 units of sodium penicillin G; 0.5 gms. of dihydrostreptomycin, and 20,000 units of bacitracin. The material was injected intramuscularly. The maximum daily dose was 2 vials, so that 40,000 units of bacitracin was the highest dose administered. The duration of treatment at this level ranged from 5 to 7 days, but one-half this dosage was used up to as long as 26 days. No toxicity was encountered. One hundred percent recovery was obtained. The combination used seems to offer the most favorable approach to the treatment of peritonitis.

EWING, M. R.: *Proctalgia fugax*. B. M. J., May 16, 1953, 1083-1085.

Ewing beautifully describes the sudden, severe rectal spasm kown as "proctalgia fugax," shows that it is *merely* a spasm, not a disease, and leads to nothing worse. He emphasizes the fact that physicians are particularly prone to the unpleasant experience. Occasionally the pain is so severe as to cause syncope, and is usually followed, in most cases, by fatigue. The cause is not local or organic, so that the symptom is somewhat related in nature to a painful spastic colon, though more severe, more sudden in onset and more prone to disappear quickly. The best way to relieve the pain is to eat something or even merely drink some water, as this brings into action the gastro-colic reflex which in some way at once stops the pain.

SACHS, M. D.: *Visualization of the common duct during cholecystography*. Am. J. Roentgen., Rad. Ther. and Nuclear Med., 69, 5, May 1953, 745-768.

Sachs, following the fatty meal, takes many films at about 8 minute intervals during the first half-hour, using rapid exposures and a special position of the patient. The use of prostigmine, by its action on the sphincter of Oddi, aids in the visualization of the common duct. Many beautiful photographs are reproduced showing the common duct during cholecystography.

LUNDMARK, V. O., METHENY, D. AND SANDERSON, E: *Intestinal perforation due to ingestion of foreign bodies*. Northwest Med., 52, 5, May 1953, 380-382.

In the present series, perforation was usually in the terminal ileum and due to fish bones, tooth picks and a bristle from a tooth brush. The wearing of artificial teeth makes it easier for a person to swallow a foreign body without knowing it.

BURT, L. I.: *Observations on biliary calculus ulcerating into the small intestine*. M. J. Australia, March 28, 1953, 444-445.

Burt has operated on seven persons in whom a gallstone had ulcerated into the small intestine. Bowel obstruction by the stone is relieved by opening the bowel and removing the stone. The symptoms of gallbladder disease are completely relieved in the first few months. As long as the fistula remains open, the patient will suffer no symptoms unless a new stone forms, or cholecystitis occurs, or the pancreas becomes diseased. Cholecystectomy does not need to be done unless such symptoms occur.

LECLUYSE, R.: *Therapy in digestive allergy*. Acta Gastro-enter. Belgica, 16, 4, 195. April 1953.

The author gives the principles in therapy:

1) Change of the ground on which allergy develops: for this purpose one prescribes daily a series of empirical therapeutics (hyposulfites, calcium, milk in parenteral way, autohemotherapy, etc.).

2) Therapy trying to avoid the conflict antigen-antibody.

a) Investigations to find the antigen, and suppress it.

b) Pesudo desensitization, specific if possible, or aspecific. (Desensitization by mouth, or parenteral, peptone, vaccine).

c) An attempt be made to avoid the formation of antibodies. (Nitrogen mustard, ACTH?)

3) If the conflict antigen-antibody happens, minimization of the effects of the allergic reaction by means of antihistaminic drugs, hormonotherapy by ACTH or cortisone.

Franz J. Lust.

BUYSSENS, N.: *Endoscopy in digestive allergy*. Acta-Gastro-enter. Belgica 16, 4, 167, April 1953.

In the esophagus, the existence of an edema which closely resembles angioneurotic edema has been noticed. Good therapeutic results with antihistaminic drugs are mentioned. In the stomach, two types of lesions are seen: atrophic gastritis with congestion, haemorrhages and sometimes erosions in the more recent cases or in acute exacerbations of chronic cases. Experiences on dogs confirm the findings. Attention is drawn upon the localization of the lesions at the antrum and the angulus. The existence of a pure functional allergy without mucosal lesions but with strong peristalsis is stressed. Except for ulcerative colitis, endoscopic examination of the rectum in allergy has been negative.

Franz J. Lust.

LEROUX, G. F. AND RUYTERS, L.: *The possibilities of a roentgenological diagnosis in allergic digestive disorders*. Acta Gastro-enter. Belgica 16, 4, April 1953.

The authors review the lesions which could be detected by roentgenology. They have considered successively the radiological aspects involved by motility, secretory and edematous modifications in the digestive tract itself and in the gallbladder.

The authors have come to the conclusion that these aspects are not specific, and propose defining the criterium to be applied during the experimental releasing of the anaphylactic crisis.

Franz J. Lust.

LEDERER, JEAN AND SPYCKERELLE-GELDERS, MARIE-HENRIETTE. *Pathogenesis of Allergy*. Acta Gastro-Enterologica, 16, 4, Special Edition, April 1953.

The meaning of allergy is discussed. The antigens are usually proteins of a high molecular weight. But some rather simple bodies may act as an antigen (Haptens).

The antibodies are gamma-globulins. They are formed either by the reticulo-endothelial system or by the lymphocytes or plasmocytes. It has been made possible to show the occurrence of antibodies by injection of the antigens in the skin, by passive sensitivation or by the fixation of the antigen on red blood cells.

It has been established that the antibodies may circulate in the blood or that they may be located in the tissue cells. In the first case after the administration of the antigen, the shock is almost instantaneous, in the other case, the reaction is delayed.

The symptoms of allergy are determined by the combination of the antigen with the specific antibodies. As a rule, histamine is then set free. The antigens may enter the body through the alimentary tract or reach the digestive system through the systemic circulation. The relations between allergy and the adrenal cortex are outlined.

The allergic man and the adrenalectomized animal behave alike in some way. But cortisone and the antihistaminic drugs differ almost completely in their pharmacodynamic peculiarities. Cortisone acts only on tissular allergy, while antihistaminic drugs alleviate the reactions of allergic shock.

Franz J. Lust.

FIRKET, J., CONRAD, V., LECOMTE, J.: *Study of the anatomical and experimental allergic reactions.* Acta Gastro-Enterologica Belgica 16, 4, 235-281, April 1953.

Acute digestive phenomena (hyperperistaltism, mucus hyper-secretion congestion of the mucous membrane with an edema sometimes directly appreciable) are often accompanying the anaphylactic shock in man.

The same gastro-intestinal phenomena ascertain the course of the affections whose allergic nature is revealed by their well defined starting agent and accompanying symptoms such as rheumatoid purpura. The reality of a response of the digestive tract to the allergic aggression is thus so established. We were only able to isolate for sure, in the course of our analysis of the microscopic criteria of tissue reactions, presumptive signs in favor of the allergic origin of such or such syndrome, and only when considering these criteria as a whole.

The lack of precision of a functional symptomatology of banal appearance and the absence of specificity of the studied lesions compel the physician to restrict his statement of the allergic nature of any gastro-enteral affection to the case when he is in possession of a particularly convincing collection of clinical and humoral arguments. They must comprise positive familial and personal antecedents, the reproduction of the digestive disorders by the introduction of the incriminated substance, their regular vanishing by its eviction, and, at last, the detection of antibodies either circulating or tissular, by tests clinically appropriate to the phenomenon under study.

However rigorous those requirements may appear, they are essential to make possible a proper reply to the question: "allergy or not." There is too much similitude, indeed, between those tissular and functional reactions that are obtained during specific allergic manifestations and those of the aspecific strain provoked by violent stress. Too many pharmacodynamic actions are devolved to substances known as antihistaminic or antiallergic for an argument to be possibly constructed on their therapeutic power in favor of a given pathogeny.

In addition to the main acute anaphylactic syndromes whose digestive reactions are nothing but symptoms among an obvious entirety (anaphylactic shock, edema of Quincke, generalized urticaria) or the main reaction to the parenteral introduction of an antigen duly identified by specific lesions (gastric or enteric Arthus), few syndromes will resist to criticism, with perhaps the exception of Schonlein-Henoch's anaphylactoid purpura.

Local digestive reactions will be of a still more difficult etiologic diagnosis. Of course, when they meet the above criteria, the gastric ulcus, intestinal infarction, gangrenous cholecystitis, regional ileitis, necrosing appendicitis, may reveal an allergic origin. But, under the present condition of our knowledge in the matter, we are unable to conclude from the particular to the general and to affirm, for each of them, a pathogenic unity that does not seem to exist at all.

Franz J. Lust.

MASSION, J., GODART, J., LEONARD, P., VAN LEBERGHE, R. AND JAMAR, J.: *Some clinical aspects of digestive allergy.* Acta Gastro-enter. Belgica 16, 4, 289-345. April 1953.

In opposition to the acute manifestations of digestive allergy, relatively easy to recognize, the digestive troubles of chronic allergy are rather difficult to diagnose. The diagnosis of chronic digestive allergy is of a clinical order, for the clinician has to evaluate the skin tests along with the anamnesis, the essential facts of which are studied along with the skin tests but the elimination diet is diagnostic. Skin tests are positive in a limited number of cases only.

In the mouth, the vesicles are a frequent sign of allergy. The same holds true for stomatitis of a contact reaction. In the esophagus, an unexplained dysphagia compels one to look for allergy. As for the stomach and duodenum, the insufficiency of hydrochloric acid plays a favoring role. The symptoms in the chronic forms consist essentially of, either periodic vomiting or pylorospasm, or a burning sensation. Pains are seldom found. The gastro-duodenal ulcer does not seem to be an allergic condition except in certain cases where allergy contributes to its occurrence. Gastroscopy is a valuable help. As for the duodenal bulb, radiology with the allergen has been found useful. Liver and bile are studied separately. On the allergic bile cyst of the animal, contractile and inflammatory reactions are noted, common to allergic reactions. In clinical practice, the cystic crises take on a peculiar form: the cystic duct and the spincter of Oddi may react in their turn. It is difficult to codify the radiology in the digestive allergy. In some sequaele of cholecystectomy, a microbial factor might intervene through an allergic mechanism. The liver is necessary to the occurrence of an allergic shock. The allergic liver crisis and the edematous hepatitis of intolerance are classified with the allergic reactions in man. The biology of the liver allergy does not show any insufficiency within the classical meaning of this term. Perhaps signs of functional hyperactivity should be sought. Normal or exaggerated functions of the liver

also seem in the experiment to be conditions necessary for the production of liver allergy.

As for the intestine, purpura fulminans and some cases belonging to the surgical pathology (mesenteric infarcts) are of an allergic origin. The acute allergic entero-colitis will be easily recognized. As for the chronic disorders, their very common symptomatology (ballooning, spasm, hypersecretion, rarely bleeding) make them both more frequent and less easy to demonstrate. Radiology with the allergen is a good sign of allergy. In the colon, the intervention of the microbic flora complicates the problem. In the early dumping syndrome in patients after gastrectomy, allergy seems to be part of the problem, as in small intestinal specimens of such cases, signs of an allergic disorder were found.

Franz J. Lust.

WIGH, RUSSELL AND SWENSON, PAUL C.: *Photofluorography for the detection of unsuspected gastric neoplasms.* Am. J. Roent. Rad. Ther. 69, 2, 242. Feb. 1953.

The authors report of a survey of 5,341 cases, of which over 3,000 came from the Cancer Detection Clinics and 1,000 were self-referred. In this group three cases with proven carcinomas were found, a fourth case was indefinite. Besides, seven cases of benign adenomas were found and operated upon. One case of advanced gastric carcinoma would have been found at any examination, the patient was inoperable. The authors calculate the cost of a single Schmidt-Helm photofluorographic examination at $1.46. The total cost of uncovering each silent tumor was $1,068-.00. The cost to find each intra-abdominal malignant neoplasm was nearly $3,000.00 and the cost for each gastric malignant neoplasm was nearly $4,000.00.

The authors conclude that the need for a method for use in the early detection of gastric neoplasm is not debatable. Previous roentgenoscopic detection methods, and other evidence, have indicated that the survival rate for persons who have concealed gastric cancer far exceeds that for symptomatic patients. The authors consider this experiment safe, accurate, suitable for large population groups and inexpensive, in spite of the above mentioned results.

Franz J. Lust.

BRUWER, A. AND HODGSON, J. R.: *Intestinal obstruction in fibrocystic disease of the pancreas.* Am. J. Roent. Rad. Th. 69, 1, 14, Jan. 1953.

Calcification in the abdomen of a newborn child is, for practical purposes, indicative of a previous fetal peritonitis due to one of a number of causes. It should be stressed that one of these causes, with or without calcification, is intestinal obstruction complicating fibrocystic disease of the pancreas. The importance of recognizing fibrocystic disease with complicating intestinal obstruction as a cause of peritonitis with calcification is that the outcome after surgical treatment of meconium ileus, with or without associated volvulus or atresia, is no longer uniformly fatal. There is strong evidence that atresia of the bowel in cases of fibrocystic disease of the pancreas is secondary to impaction of meconium, rather than a primary embryologic manifestation.

Franz J. Lust.

CHAPTAL J. (MONTPELLIER) *Pathology of the Pylorus in Nurslings.* Arch. Mal. App. Dig., Mar., No. 3, 1953.

1. *Syndromes of Functional Disorder of the Pylorus.*

In the case of nurslings, these are two in number: (a) *Pylorospasm or spasm of the pylorus*: major form of the disease with continual vomiting recorded by Marfan, of fairly frequent occurrence, arises from a neuro-vegetative disequilibrium of constitutional origin.

A very early gastric intolerance of food, with a slight lowering in general fitness, develops a spontaneous cure by the fourth or eighth month. Diagnosis is confirmed by the radiological syndrome of interrupted evacuation of the stomach (Barret and Chauffour 1922). Pylorospasm should be distinguished from organic disorders (stenosis of the pylorus, cardiotuberositary malposition) and from functional syndromes: vomiting due to aerophagia, dyspepsia due to hyper or hypo-sensitivity of the stomach . . .

Careful dieting, the addition of bulk to meals in the form of carob seeds, gastric sedatives (atropine, gardenal) are the most important therapeutic indications.

(b) *Spasm of the pylorus through dyspepsia accompanying infectious parenteral conditions*: isolated by Czerny, this also arises, as the work of Maurice Renaud, Ribadeau, Dumas and Reilly has shown, from toxi-infectious changes in the neuro-vegetative system, in its centers as in its peripheral branches in the most varied types of infection.

2. *Organic Disorders.*

These are represented in the main by hypertrophic stenosis of the pylorus (ulcers and cancers being completely eliminated from this study).

Hypertrophic stenosis of the pylorus is characterized anatomically by hyperplastic hypertrophy of the muscular layer of the pylorus. The spasm associated with this accounts for the variations in the intensity and in the gravity of the disorder.

The frequency of cases in the same family, the comparison of twins, the coexistence of various congenital malformations authorize the interpretation of hypertrophic stenosis of the pylorus as a genic complaint whose mode of transmission is complex (M. Lamy).

The syndrome—set up usually after a *free interval*—is characterized by difficulty and slowness in evacuation of the stomach, peristaltic contractions of the organ, vomiting, progressive stasis, emaciation and dehydration, rarely by the appearance of the gastric "olive." Chloropenia, alkalosis and hypokalemia are the humoral signs.

Radiology reveals the indirect (disorders in transit) and direct signs (tumoral image: Runstrom, Wallgren and Andersen). It is the essential element in diagnosis.

Development, if the disorder were left to itself, would be towards progressive denutrition, aggravated by intercurrent infections.

Treatment on the other hand has a consistently favorable influence on prognosis:

—whether it be exclusively *medical* (Usener, Monnod, Rinvik, Wallgren . . .) by antispasmodics (bromhydrate of methyl nitrate of atropine);

—or *surgical*, by extra-mucosal pylorotomy (Fredet 1910). This method, which is perfectly safe, has up to the present time prevailed to a great extent in France.

POLIOMYELITIS RECOGNIZED AS A WORLD-WIDE DANGER

WHO Experts Meeting in Rome Draft International Program

The first session of the WHO Expert Committee on Poliomyelitis, held under the chairmanship of Dr. John R. Paul of Yale University, took place in Rome from 14 to 19 September, attended by scientists from Canada, France, Great Britain, Israel, South Africa, Sweden and the USA.

Recognition that poliomyelitis is a threat of world-wide significance led WHO to call, for the first time, an international group of experts to draft proposals for a world-wide program of research on the polio viruses, and for the development and application of control measures.

The first world program for polio research was outlined in a report developed by the Committee. The first step recommended is designation by the WHO of a number of research laboratories in all continents, to work as WHO regional laboratories.

A list of urgent research projects was also drawn up. This list stresses the fact that the paralytic form of the disease is increasing and that "unless effective measures for its control are introduced, it is reasonable to assume that polio will present an increasingly serious problem in almost all countries of the world."

The Committee report adds that transformation of the relatively uncommon "infantile paralysis" of the nineteenth century into epidemic polio, which is now almost worldwide, is one of the most formidable problems facing public health today. What causes particular concern is the complete failure so far to control the disease.

Commenting on the use of gamma globulin, the Committee stated that "its practical application as a prophylactic in polio is greatly limited. The Committee condemns its widespread and indiscriminate administration to people who have had no known contact with cases of poliomyelitis."

A more promising method of control is possible by the use of prophylactic vaccines which "may become available to health officers in the not too distant future." Vaccination, however, is still in the experimental stage and more research needed, the Committee report states. Stressing polio as highly infectious, the experts recommended immediate isolation and quarantine measures for paralytic cases in the communities adding that the restriction of international travel is not justified.

Five recommendations are made to health authorities:

1. Avoid operations including the removal of tonsils and adenoids during an epidemic.

2. The activity of sick people suspected with polio should be restricted for one week.

3. Those near polio cases should take a minimum amount of exercise for up to twenty-one days after exposure and avoid fatigue.

4. Diphtheria and pertussis vaccination should normally continue during the polio season, but not during an epidemic.

5. Avoid the large-scale use of intra-muscular injections of an irritant character.

The report goes before the WHO Executive Board next January for approval for publication.

BIOMYDRIN

A team of Chicago scientists reported recently the clinical use of a new drug that destroys at least eleven identifiable bacteria when used in the treatment of acute and chronic sinusitis and infectious and allergic rhinitis and which has indications of being effective in the prevention of some nasal infections.

Dr. A. M. Lazar and M. Goldin, of the department of Otolaryngology of Chicago Medical School, and Mt. Sinai Medical Research Foundation, Chicago, reported the completion of 124 clinical cases of various types of nasal infections in a study employing the new drug, Biomydrin, with 91.1% of the cases showing definite improvement. Biomydrin is a nasal spray which is available on doctor's prescription.

Dr. Lazar, Assistant Professor of Otolaryngology at Chicago Medical School, and Mr. Goldin, research bacteriologist, reported that the new nasal medication not only halted growth of a wide range of harmful bacteria known to infect nasal passages, but also was effective in killing at least eleven separate types of bacteria which caused a variety of upper respiratory ailments in an unselected group of patients used in the tests.

The scientists, reporting in the scientific journal, Eye, Ear, Nose and Throat Monthly, for September, said that Biomydrin produced sterile cultures from nasal mucosa in 37% of cases treated. This continued for as long as two days after discontinuance of treatment with the drug. "We can assume, therefore, that the potency of Biomydrin renders the nasal passages sterile for at least 48 hours," Dr. Lazar said in commenting on the paper, "thereby demonstrating its value as a preventive drug against certain sinus infections during that period."

(Biomydrin is a development of extensive research at Nepera Chemical Co., Inc., Yonkers, N. Y., and it contains a significant new bactericidal drug, thonzonium bromide, which spreads the other components of the solution throughout the minute, otherwise inaccessible crevices of the nasal passages.)

"It is recognized," the investigators reported, "that the indiscriminate use of decongestant nose drops is an unwise procedure and patients too frequently use them with no knowledge of their limitations and contraindications.

"It is true also, however, that the judicious use of a properly formulated nasal solution under the supervision of a physician can be of inestimable value . . . The nature of the nasal solution is obviously the most important single factor in determining the wisdom of its use. We feel that a properly constructed solution containing a combination of blood vessel constrictor, antibiotic and antihistaminic could be of great use, provided it demonstrated the required degree of effectiveness without any untoward side reactions.

"We have recently had occasion to become acquainted with such a nasal solution (Biomydrin) which, from purely theoretical considerations, appeared to fulfill many of these requirements. It consists of a combination of neomycin, gram-

icidin, thonzonium bromide, the antihistamine thonzylamine hydrochloride, and the potent vasoconstrictor, phenylephrine hydrochloride, properly buffered and at the physiologic pH for intranasal membrances of 6.2, packaged in a disposable plastic 'squeeze bottle' capable of delivering a fine spray or in plain bottles for use with a dropper or power atomizer."

During the winter of 1952-53 a group of unselected patients with upper respiratory tract infections was studied clinically and bacteriologically and cultures on 97 of these patients were obtained from the nasal passages before treatment was begun. Cultures were inoculated and organisms were identified by the usual bacteriologic technics.

The tests were conducted in connection with the Mt. Sinai Medical Research Foundation, a nonprofit organization associated with the Chicago Medical School and Mt. Sinai Hospital in Chicago. The Foundation, organized in 1946, is dedicated to important fundamental research in various fields of the biological sciences.

Patients were given one week's supply of Biomydrin with instructions to spray two or three times into each nostril up to five or six times a day for the ordinary case. Children were given one to two sprays, four to five times a day.

"The spray was soon found to be preferable to drops from the standpoint of patients' acceptability," the reporting scientists said, "and, since it provided maximum coverage of the nasal mucosa, has been used almost exclusively."

Patients were re-examined clinically within two days after medication was completed and repeat cultures were taken at this time whenever possible, with a total of 124 patients studied in this manner.

"The patient's acceptance of the drug, in general, was excellent," the report said, "and in many cases, enthusiastic. Complaints relative to stinging sensations, nausea, excessive drying, or untoward reactions were rare. Most of the patients found at least partial relief of their symptoms within a few minutes after medication was administered."

The table of results which the scientists compiled and which indicates definite amelioration of nine distinct nasal conditions is based "not on the complete eradication of the pathologic condition, but on definite symptomatic relief, which, in the final analysis is all that a nasal solution can be expected to do," the doctors said. "However, the failure to observe relapses after treatment was discontinued would seem to indicate that more than mere symptomatic relief had been accomplished.

"It is apparent from all of these results," the report said, "that Biomydrin is highly active against a wide variety of both gram-positive and gram-negative organisms associated with nasal infections, and that its activity is mainly bactericidal, rather than merely bacteriostatic.

"It is also notable that the drug is effective *in vitro* against such notoriously refractory organisms as *Pseudomonas aeruginosa* and *Proteus*—organisms which fail to succumb to the effect of so many antibiotics and other chemotherapeutic agents. These germs are considered scavengers which are difficult to eradicate. This fact is emphasized since, with the common usage of antibiotics, the prevalence of these gram-negative organisms in the upper respiratory tract has undoubtedly been steadily increasing.

"It is noticeable that there was a marked reduction in the number and type of bacteria from the nose after medication even in those cases where the nasal tissues had previously been heavily infected, but other factors besides this reduction undoubtedly play a role in recovery. The large number of sterile cultures found after treatment is particularly striking and affords objective evidence of the potency of the chemotherapeutic activity of the drug. Even though such a sterile culture must be considered a transitory condition, the persistence of sterile cultures for as long as two days after discontinuance of treatment is difficult to explain without the assumption that the properties of Biomydrin are such as to cause it to persist at the site of its application for a prolonged period of time."

In summarizing the results of their study, Dr. Lazar and Mr. Goldin said, "Biomydrin has been found to be of great value in a wide variety of these conditions from the standpoint of effectiveness, safety and patient's acceptability. The material is a potent antibacterial decongestive drug and is virtually free of the danger of sensitization. Nasal cultures of 38% of patients treated with Biomydrin proved sterile after a short course of application of the drug. Our successful experience with Biomydrin leads us to the recommendation that, properly used, it will establish itself as a very useful addition to nasal remedial agents."

ANTIHISTAMINE EFFECTIVE AGAINST HAY FEVER ALSO PROVES VALUABLE IN TREATING MOTION SICKNESS

Persons experiencing nausea while riding in steamships or airplanes have obtained dramatic relief and in many cases avoided severe discomfort entirely after administration of an antihistaminic drug, it was announced by Wyeth Laboratories.

Dr. Daniel L. Shaw, Jr., of the Wyeth Medical Department identified the antihistamine as Phenergan Hydrochloride, used in the treatment of most allergies and found particularly effective for the relief of hay fever last year.

Detailed experiments by research groups, including the U. S. armed services, have established the value of the drug, Dr. Shaw said.

In an aerial test by the U. S. Air Force, in which actual vomiting was used as the criterion, only 2 per cent of 510 soldiers given Phenergan before their flights experienced nausea sufficient to cause regurgitation. By comparison, 6.8 per cent of soldiers treated with inert drugs on the same flight became sick to the point of vomiting.

Similar results were noted at sea. On an 11-day trip across the North Atlantic in winter, Phenergan was found effective in a test group, reducing the incidence of regurgitation below that found in another group treated with a drug currently in widespread use.

No drug has been found to eliminate the queasy stomach entirely, Dr. Shaw said. He added that all drugs now being used cause undesirable side effects, the chief one being drowsiness. Phenergan, providing a longer-lasting protection

than other currently available drugs, can be given in smaller and less frequent doses, considerably reducing the drowsiness.

Phenergan may be dispensed only by prescription, in common with all other antihistaminic agents of similar potency, Dr. Shaw said. For the guidance of physicians, Wyeth is recommending that patients be instructed to take one 25 milligram dose 30 to 60 minutes before embarking on a ship, and repeat the dose eight to twelve hours later if required. On successive days of the voyage, 25 milligrams upon arising and repeated before the evening meal is deemed sufficient.

For voyages or flights less than eight hours, the single dose beforehand is usually sufficient for those who respond to the drug. But unfortunately, the doctor pointed out, a few persons are affected regardless of treatment, including those who, standing on solid ground, become ill at the mere sight of a tossing sea.

Exact cause of motion sickness is not known, but the malady has been traced to the middle ear, which reacts strangely whenever the body's position is changed by agents beyond its control. The exact effect of antihistamines upon the middle ear is not known either, but results of the many tests are clear, Dr. Shaw concluded.

AD CAMPAIGN SEEKS NEW MEMBERS FOR WORLD MEDICAL ASSOCIATION

New York, N. Y.—The biggest advertising campaign yet designed to encourage American doctors to join the United States Committee of the increasingly important World Medical Association is under way with the participation of the leading medical advertising agencies.

The world group is devoted to the interests of freedom in medicine and to the exchange of new medical experience. It is also noted for extensive research projects and studies of the educational requirements everywhere.

Contributing to the campaign are: L. W. Frohlich and Company; William Douglas McAdams; Noyes and Sproul; Cortez Enloe; Paul Klempner; and Robert Wilson.

These agencies formed a committee to work with the World Medical Association.

Layouts of the advertisements are being done at L. W. Frohlich. Copy is being prepared by Cortez Enloe. Medical journals are contributing space; for example, most of the state journals donated one page a month for eight months.

"What affects world medicine affects you" and "This is your only voice in world medicine" are the themes. Advantages of membership to civilian, military and retired physicians are emphasized.

Letters of introduction to foreign groups for use during trips; representation before the World Health Organization and others; and quarterly Bulletins reporting medical advances, are incentives.

PREVENTION OF TRANSFUSION REACTIONS

Offenkrantz, F. M.; Margolin, S.; and Jackson, D.: Prevention of transfusion reactions by intravenous Chlor-Trimeton, J. M. Soc. New Jersey 50:253 (June) 1953.

The efficiency of the antihistamine Chlor-Trimeton in preventing allergic and pyrogenic reactions in transfusions through introduction directly into the blood prior to infusion has been conclusively demonstrated in tests made by Offenkrantz and associates.

In a varied and totally unselected series of 300 transfusions with 10 mg. of Chlor-Trimeton there developed not a single incidence of allergic reaction and only 0.6 per cent pyrogenic.

Contrarily, a control group of 350 patients receiving transfusions without Chlor-Trimeton instanced 22 pyrogenic or allergic reactions, or both—a rate of 6.3 per cent.

In spite of improvements in blood-typing techniques and the use of individual, disposable infusion sets, the incidence of transfusion reactions, almost all of which are allergic or pyrogenic, continues to range from five to more than ten per cent. In warm climates the incidence may be even higher because of hemolysis resulting from refrigeration difficulties and the associated increase in breakdown products.

Offenkrantz and associates feel that the tests prove beyond any doubt the efficiency of this procedure in blood transfusions.

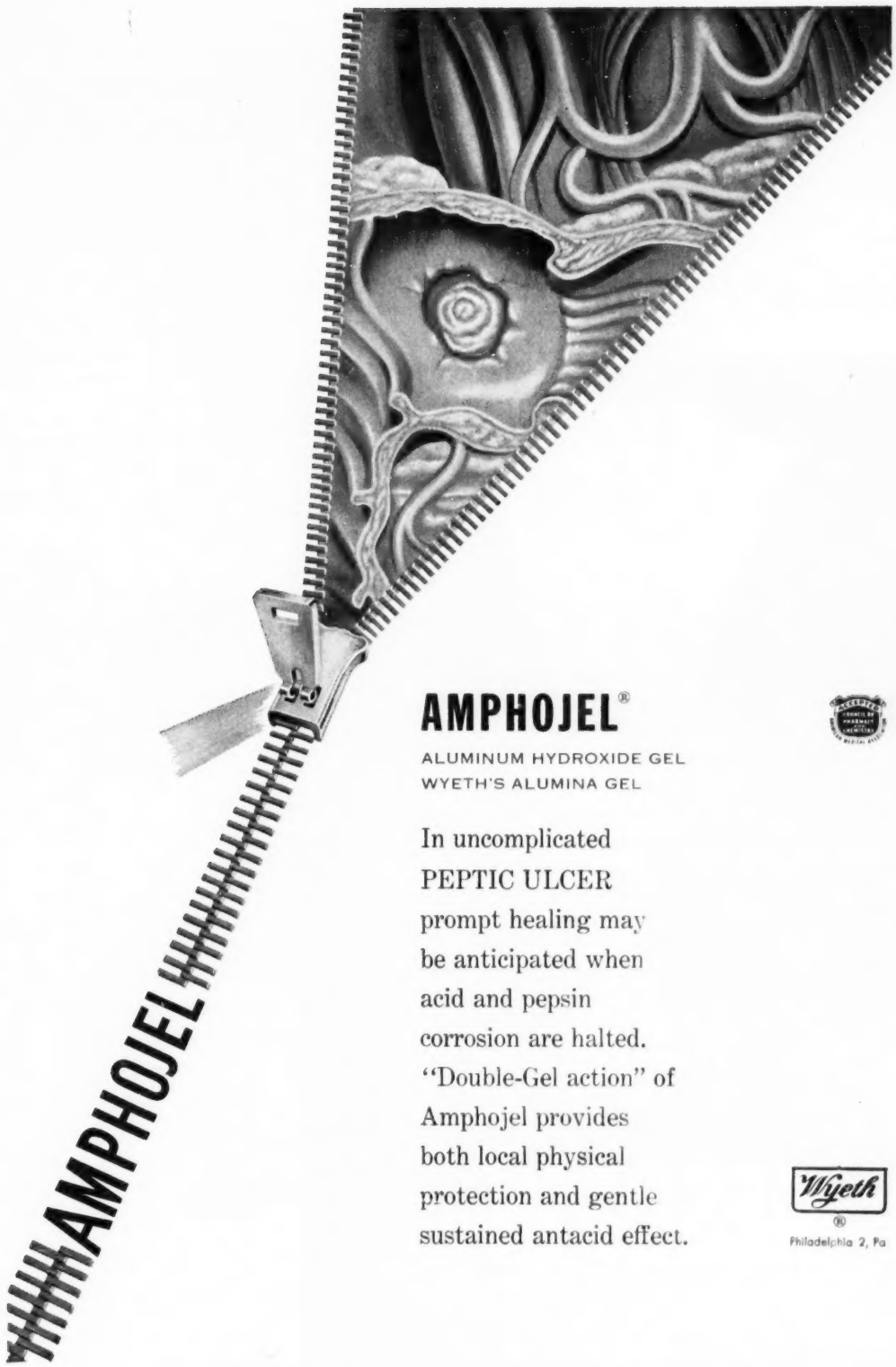
DR. M. G. CANDAU TAKES OFFICE AS DIRECTOR GENERAL OF THE WORLD HEALTH ORGANIZATION

Dr. Brock Chisholm, who retired recently from his position as Director-General of the World Health Organization, handed over the duties of his office to Dr. M. G. Candau at a brief gathering of the headquarters' staff of WHO in the Palais des Nations.

Dr. Candau, who declared that Dr. Chisholm would be greatly missed by everyone who had had the good fortune to work with him, said he counted on the support of all members of the Secretariat in the tasks which lay before him.

WHO's new Director-General, who was born in Rio de Janeiro, Brazil in 1911 received his early medical training at the School of Medicine, State of Rio de Janeiro, later going to the University of Brazil and Johns Hopkins University, Baltimore, Maryland, for training in Public Health.

From 1934 to 1950 he was in charge of various health services



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In uncomplicated PEPTIC ULCER prompt healing may be anticipated when acid and pepsin corrosion are halted. "Double-Gel action" of Amphojel provides both local physical protection and gentle sustained antacid effect.

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in Brazil including the Co-operative Health Services of the Brazilian Government and the Institute of Inter-American Affairs. From 1938-50 he was also Assistant Professor of Hygiene at the School of Medicine in the State of Rio de Janeiro.

Dr. Candau joined WHO, in Geneva, in 1950 as Director of the Division of Organization of Health Services, becoming in 1951 Assistant Director-General, Department of Advisory Services. From 1952 to the present he was in Washington as Assistant Director, Pan American Sanitary Bureau, Regional Office for the Americas.

Other positions he has occupied are: Executive Secretary, 1946-1947, and President, 1948-1949, Brazilian Society of Hygiene; and Vice-President, American Public Health Association, 1949-1950.

Dr. Candau is author of a series of scientific papers, on intestinal parasites, malaria, public health administration, bio-statistics, rural hygiene, etc.

Twenty-six grants to universities and medical centers throughout the United States and abroad for research in health and disease, amounting to $178,092.54 were reported on today by William S. Lasdon, president of the Lasdon Foundation, Inc., Yonkers, N. Y., in an eight months' report of the Foundation's philanthropic activities.

"The Lasdon Foundation is dedicated to the primary goal of humanitarian service through scientific research," Mr. Lasdon said. "The research supported by the Foundation since it was organized in 1946 covers a wide field of medical problems considered in the light of their fundamental importance to science, education, and public health.

"It is the policy of the directors of the Foundation to award grants covering selected medical projects in order to sustain research activities which might otherwise be neglected," he said.

The group of grants reported today by Mr. Lasdon include a special grant of $15,000 to Harvard Medical School for further studies into the transplantation of the human kidney, and a grant of $15,856 to Washington University, St. Louis, Mo., for research into certain phases of hypertension and other vascular diseases, under the direction of Dr. Henry A. Schroeder.

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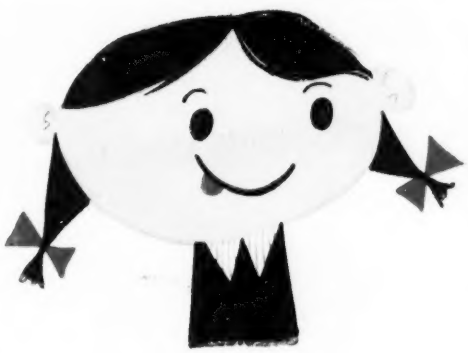

Pediatric Drops

Each cc. contains 100 mg. of pure crystalline Terramycin. Supplied in 10 cc. bottles with special dropper calibrated at 25 mg. and 50 mg. May be administered directly or mixed with nonacidulated foods and liquids. Economical 1.0 gram size often provides the *total dose* required for treatment of infections of average severity in infants.

Supplied: Bottles of 1.0 Gm.

Oral Suspension *(Flavored)*

Each 5 cc. teaspoonful contains 250 mg. of pure crystalline Terramycin. Effective against gram-positive and gram-negative bacteria, including the important coli-aerogenes group, rickettsiae, certain large viruses and protozoa.

Supplied: Bottles of 1.5 Gm.

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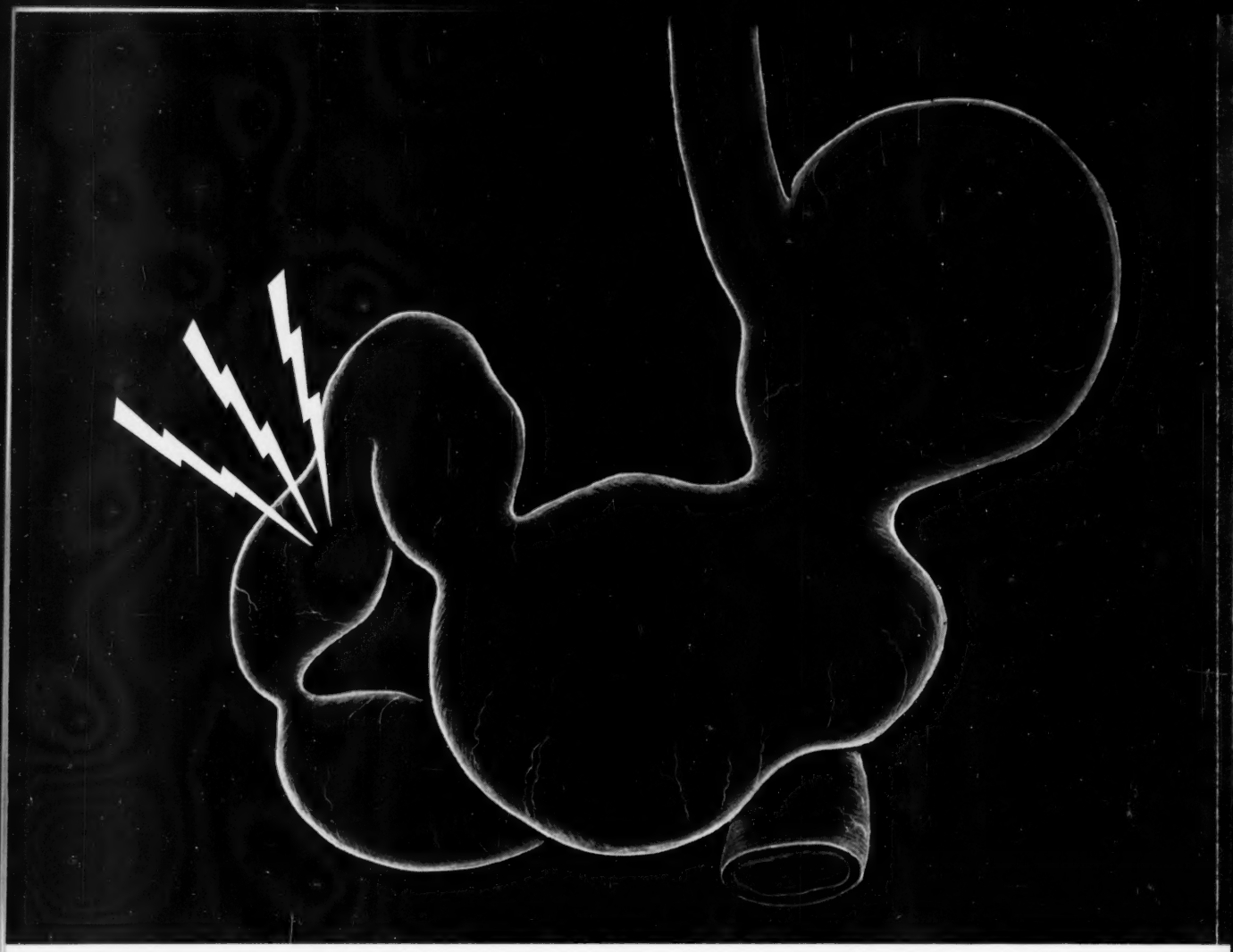

Abnormal Motility as the Cause of Ulcer Pain

Until recently the general opinion was held that ulcer pain was primarily caused by the presence of hydrochloric acid on the surface of the ulcer.

Present investigations[1,2] on the relationship of acidity and muscular activity to ulcer pain have led to the following concept of its etiologic factor:

> "... abnormal motility[2] is the fundamental mechanism through which ulcer pain is produced. For the production and perception of ulcer pain there must be, one, a stimulus, HCl or others less well understood; two, an intact motor nerve supply to the stomach and duodenum; three, altered gastro-duodenal motility; and four, an intact sensory pathway to the cerebral cortex."

Clinical Application of Pro-Banthine®

Pro-Banthine has been demonstrated consistently to reduce hypermotility of the stomach and intestinal tract and in most instances also to reduce gastric acidity. Dramatic remissions[1] in peptic ulcer have followed Pro-Banthine therapy. These remissions (or possible cures) were established not only on the basis of the disappearance of pain and increased subjective well-being but also on roentgenologic evidence.

Pro-Banthine (Beta-diisopropylaminoethyl xanthene-9-carboxylate methobromide, brand of propantheline bromide) has other fields of usefulness, particularly in those in which vagotonia or parasympathotonia is present. These conditions include hypermotility of the large and small bowel, hyperemesis gravidarum, certain forms of pylorospasm, pancreatitis and ureteral and bladder spasm.

1. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, to be published.

2. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology *23*:252 (Feb.) 1953.

SEARLE Research in the Service of Medicine